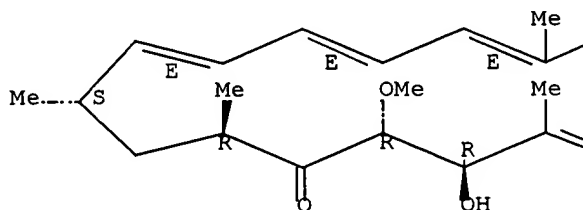


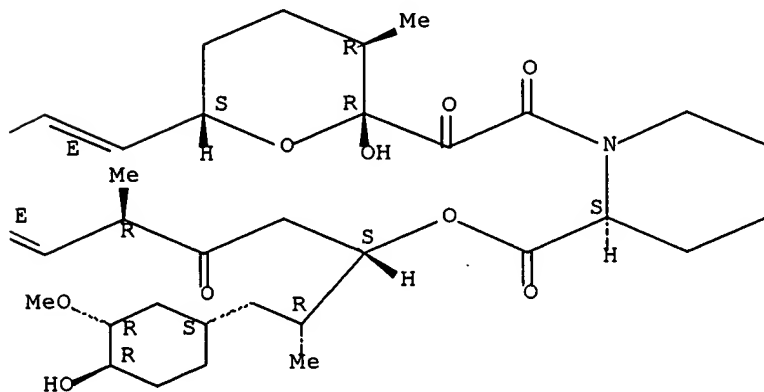
L16 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2001 ACS
 AN 1995:885467 CAPLUS
 DN 124:29473
 TI Ionization of the C7 methoxy group in rapamycin by 5 M lithium perchlorate-diethyl ether
 AU Luengo, Juan I.; Konialian-Beck, Arda; Holt, Dennis A.
 CS Dep. Medicinal Chem., SmithKline Beecham Pharm., Prussia, PA, 19406, USA
 SO Tetrahedron Lett. (1995), 36(43), 7823-4
 CODEN: TELEAY; ISSN: 0040-4039
 DT Journal
 LA English
 OS CASREACT 124:29473
 AB Treatment of the macrolide rapamycin with 5 M LiClO₄/diethyl ether promoted ionization and elimination of the C-7 methoxy group, leading to the conjugated tetraene. In the presence of electron-rich arom. systems, efficient arylation at C-7 took place. C-7 arylation of rapamycin could also be achieved with Suzuki's catalyst (Cp₂HfCl₂-AgClO₄).
 IT **158615-24-8P**
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (elimination and arylation of rapamycin with lithium perchlorate-diethyl ether)
 RN 158615-24-8 CAPLUS
 CN Rapamycin, 7,8-didehydro-7-demethoxy-, (7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as described by E or Z.

PAGE 1-A

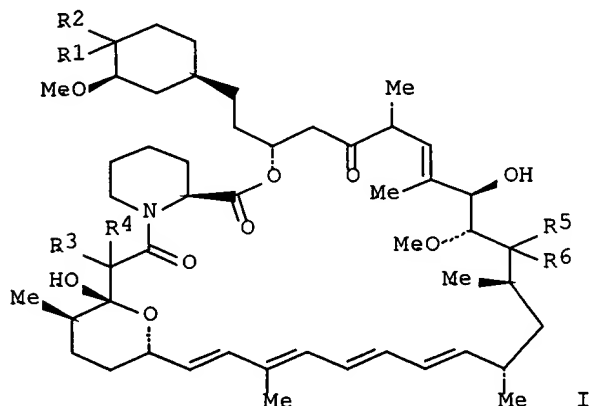


PAGE 1-B



L16 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2001 ACS
 AN 1995:255611 CAPLUS
 DN 122:132846
 TI Fungicidal and immunomodulatory rapamycin derivatives
 IN Luengo, Juan I.
 PA SmithKline Beecham Corp., USA
 SO U.S., 10 pp.
 CODEN: USXXAM
 DT Patent
 LA English
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5362735	A	19941108	US 1994-200265	19940223
	WO 9522972	A1	19950831	WO 1994-US8726	19940802
	W: JP				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	EP 754040	A1	19970122	EP 1994-924550	19940802
	R: BE, CH, DE, FR, GB, IT, NL				
	JP 10500661	T2	19980120	JP 1994-522321	19940802
PRAI	US 1994-200265		19940223		
	WO 1994-US8726		19940802		
OS	MARPAT 122:132846				
GI					



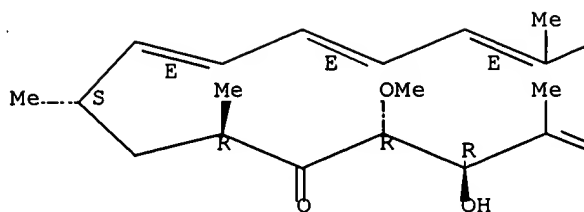
AB Rapamycin derivs. I [R1 and R2 are selected from the group consisting of :O, (OH,H) and (H,H); R3 and R4 are selected from the group consisting of :O, (H,H) and (H,OH); and R5 and R6 are selected from the group consisting of :O and (H,OH); the order of moieties in the parentheses does not suggest a particular configuration]; pharmaceutical compns. comprising such rapamycin derivs. and pharmaceutically acceptable carriers or excipients; and methods of using such derivs. to inhibit pathogenic fungi growth inhibition, inhibit immunosuppression or treat carcinogenic tumors are disclosed. The preferred compd. showed in IC12 of 7 ng/mL against *Saccharomyces cerevisiae* and IC50 of 7 nM in the mitogenesis assay. (IC12 refers to the concn. of drug in the antifungal agar diffusion assay which produces a 12 mm zone of inhibition). These results indicate that the compd. has both antifungal and immunomodulatory activity. Pharmaceutical formulations were given.

IT 158615-24-8P, 7-Demethoxy-7,8-dehydrorapamycin
 RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
 (fungicidal and immunomodulatory rapamycin derivs.)

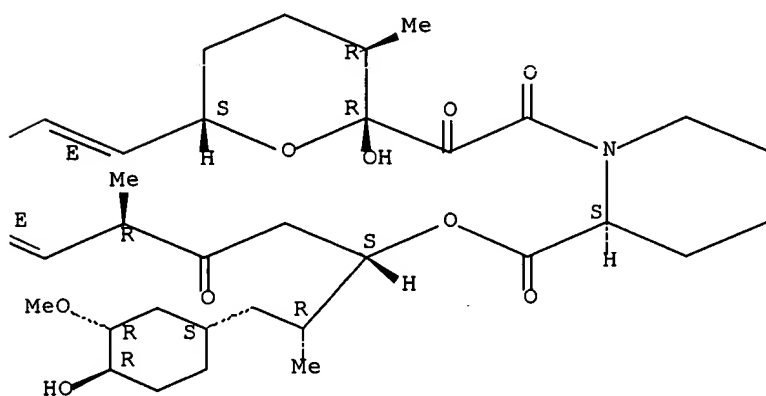
RN 158615-24-8 CAPLUS
 CN Rapamycin, 7,8-didehydro-7-demethoxy-, (7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

PAGE 1-A



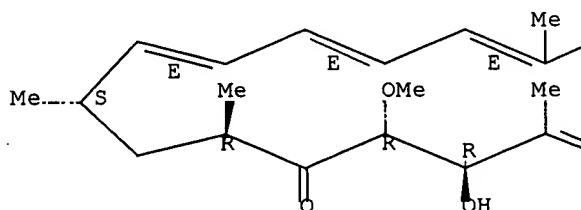
PAGE 1-B



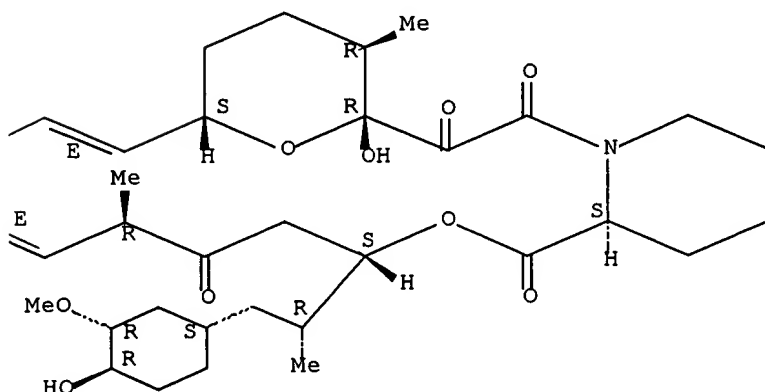
L16 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2001 ACS
 AN 1994:655475 CAPLUS
 DN 121:255475
 TI Acid catalyzed functionalization of rapamycin
 AU Grinfeld, Alexander A.; Caufield, Craig E.; Schiksnis, Robert A.; Mattes, James F.; Chan, Kelvin W.
 CS Department Chemical Sciences, Wyeth-Ayerst Research, Inc., Princeton, NJ, 08543-8000, USA
 SO Tetrahedron Lett. (1994), 35(37), 6835-8
 CODEN: TELEAY; ISSN: 0040-4039
 DT Journal
 LA English
 OS CASREACT 121:255475
 AB Rapamycin rapidly undergoes demethoxylation at C-7 in the presence of Lewis acids (BF₃.Et₂O, SnCl₄ etc.) to give a highly stabilized carbocation. This intermediate gives a tetraene or is trapped by nucleophiles to give functionalized trienes. Several examples of the substitution reaction and elaboration of the reaction scheme are reported.
 IT **158615-24-8P**
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (prepn. of)
 RN 158615-24-8 CAPLUS
 CN Rapamycin, 7,8-didehydro-7-demethoxy-, (7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as described by E or Z.

PAGE 1-A



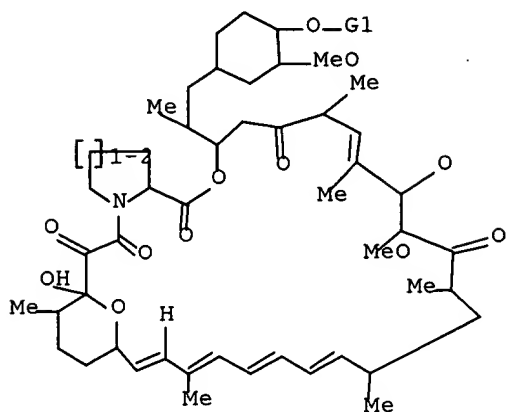
PAGE 1-B



=> d l12; d l2; d his

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L12 STR

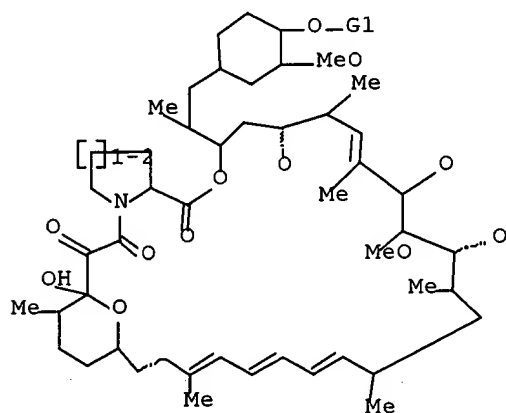


G1 H, Ak

Structure attributes must be viewed using STN Express query preparation.

L2 HAS NO ANSWERS

L2 STR



G1 H, Ak

Structure attributes must be viewed using STN Express query preparation.

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FILE 'REGISTRY' ENTERED AT 18:15:48 ON 12 APR 2001

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L2 STRUCTURE UPLOADED

L3 QUE L2 AND L1 AND L1

L4 34 S L3

L5 695 S L3 FUL

FILE 'STNGUIDE' ENTERED AT 18:16:57 ON 12 APR 2001

FILE 'REGISTRY' ENTERED AT 18:18:32 ON 12 APR 2001

L6 SCREEN 1821 OR 1822 OR 1823 OR 1824

L7 STRUCTURE UPLOADED
L8 QUE L7 AND L6 AND L6
L9 32 S L8 SAM SUB=L5
L10 624 S L8 FUL SUB=L5
L11 SCREEN 1821 OR 1822 OR 1823 OR 1824
L12 STRUCTURE UPLOADED
L13 QUE L12 AND L11 AND L11
L14 0 S L13 SAM SUB=L5
L15 2 S L13 FUL SUB=L5

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L16 4 S L15

L41 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2001 ACS

AN 2001:152693 CAPLUS

DN 134:193290

TI Synthesis and biological activity of 28-epirapalogs with reduced immunosuppressive activity for multimerizing chimeric proteins

IN Yang, Wu; Digits, Cheryl A.; Rozamus, Leonard; Holt, Dennis A.

PA Ariad Gene Therapeutics, Inc., USA

SO PCT Int. Appl., 96 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001014387	A1	20010301	WO 2000-US23334	20000824
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				

PRAI US 1999-150447 19990824

OS MARPAT 134:193290

AB Methods and materials involving synthesis of 28-epirapamycin analogs are disclosed. Thus, 28-epirapamycin is synthesized via cleavage of rapamycin with titanium tetraisopropoxide and retro aldol macrocyclization and analogs are prepd. by modification at C7 and C43. These analogs have reduced immunosuppressive activity and comparative data for FKRB binding, activity in cellular transcription assay and activity in mouse splenocyte assay are given.

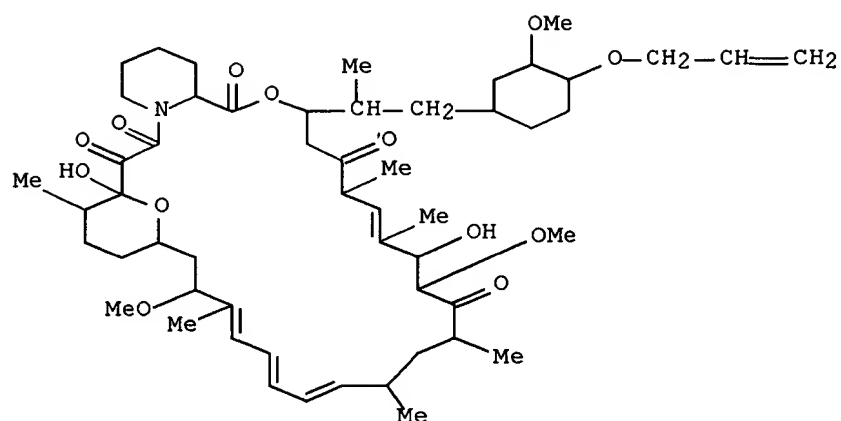
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328060-36-2P 328060-37-3P 328060-38-4P

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(synthesis and biol. activity of 28-epirapalogs with reduced immunosuppressive activity for multimerizing chimeric proteins)

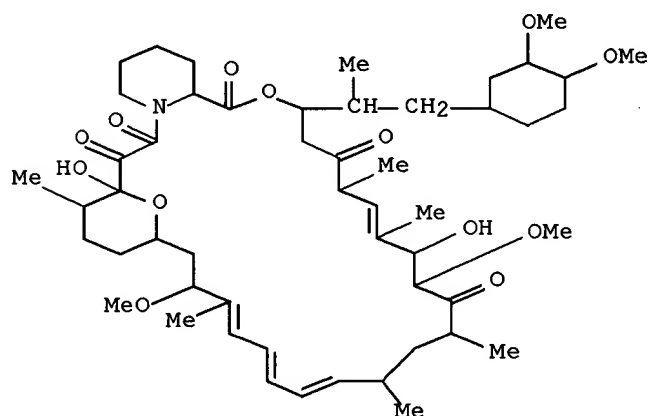
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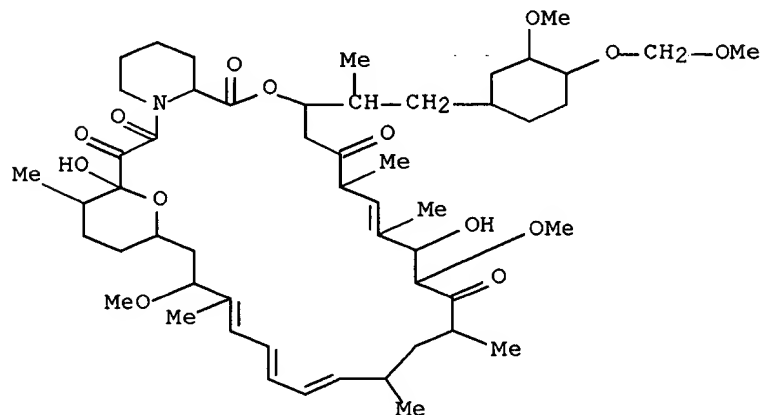
RN 328059-77-4 CAPLUS

CN Rapamycin, 42-O-methyl-, (31S)- (9CI) (CA INDEX NAME)



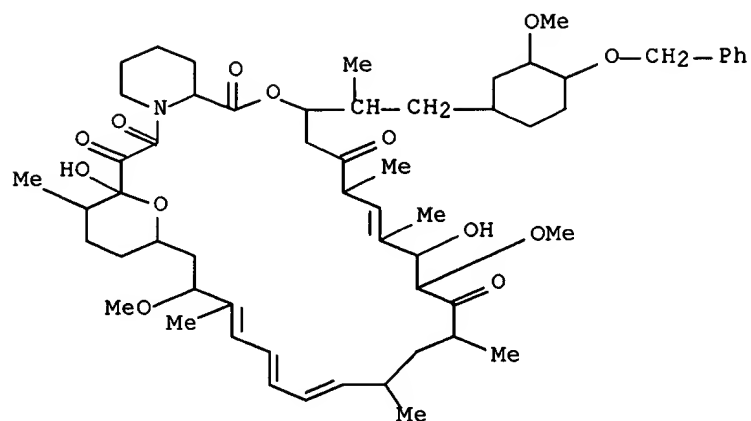
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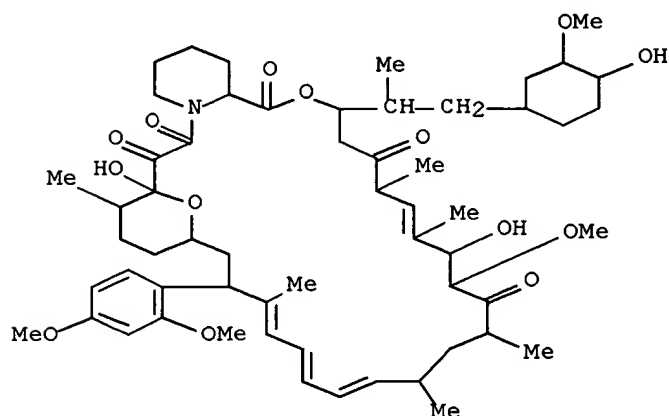
RN 328059-79-6 CAPLUS

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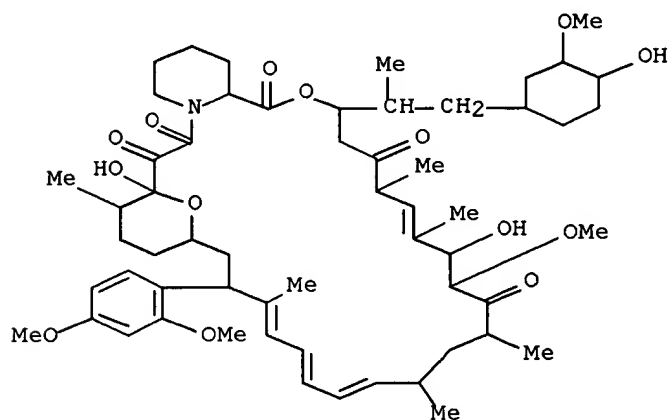
RN 328059-80-9 CAPLUS

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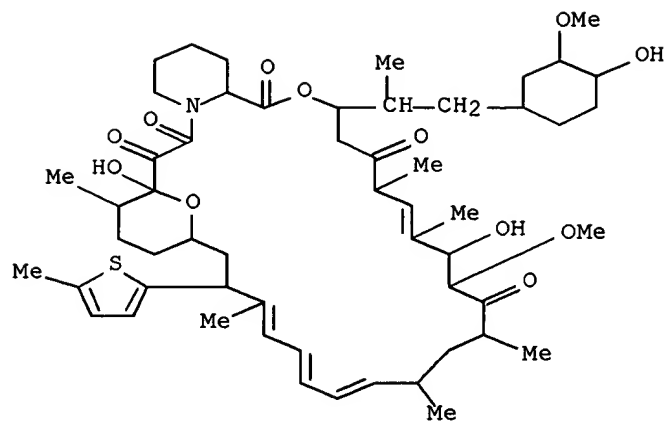
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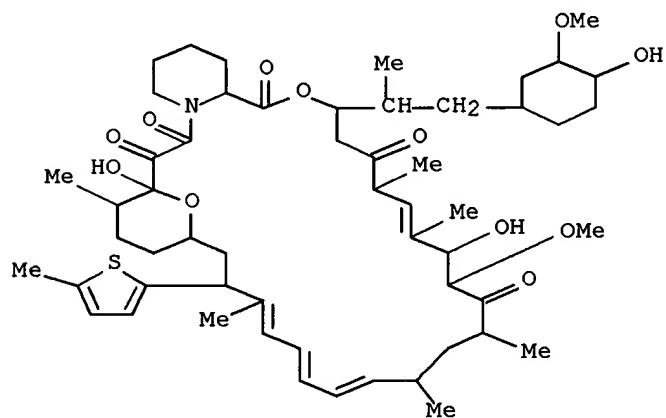


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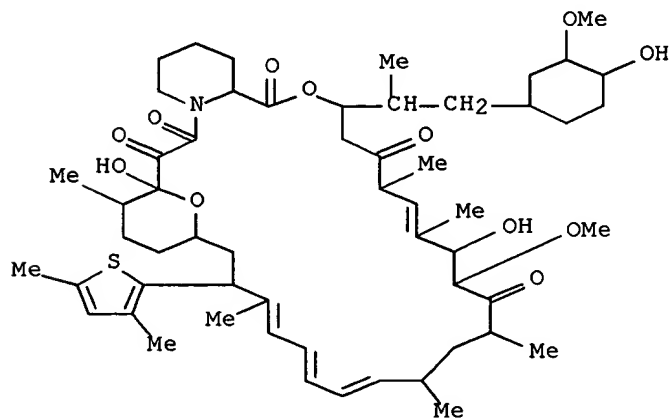
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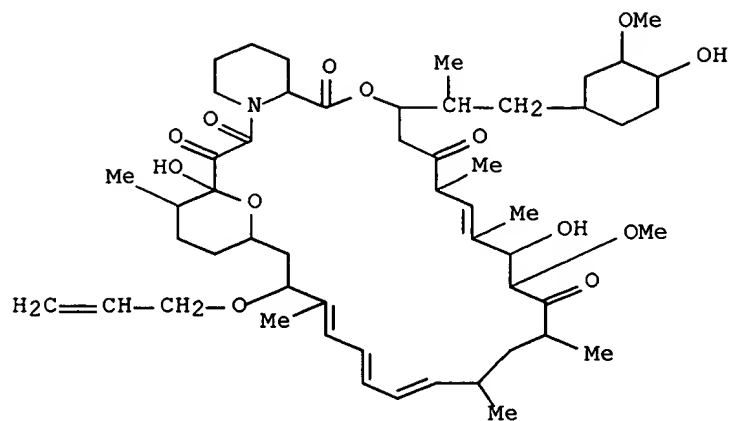
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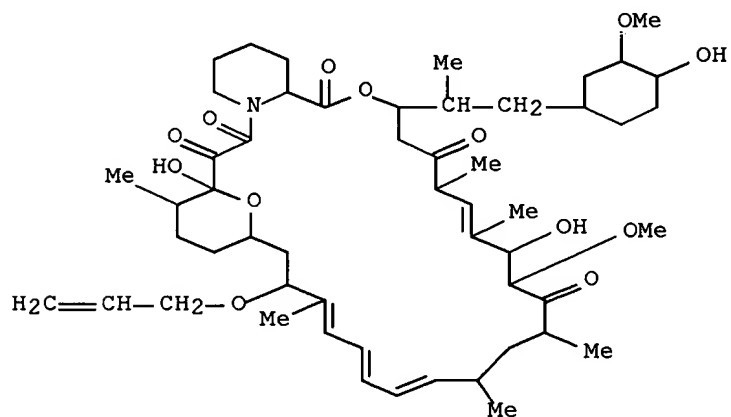


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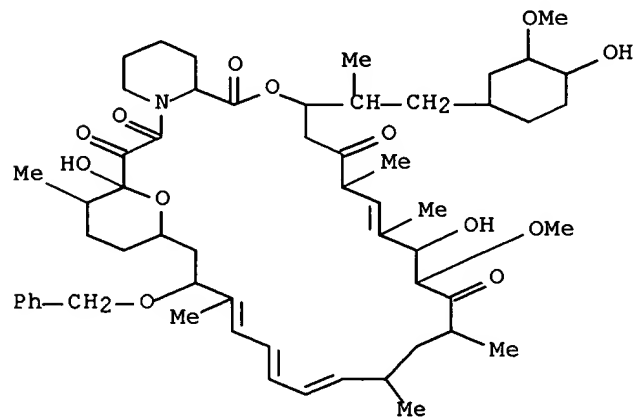
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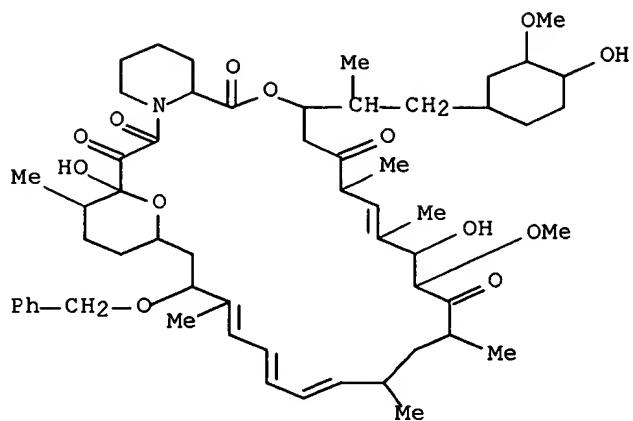
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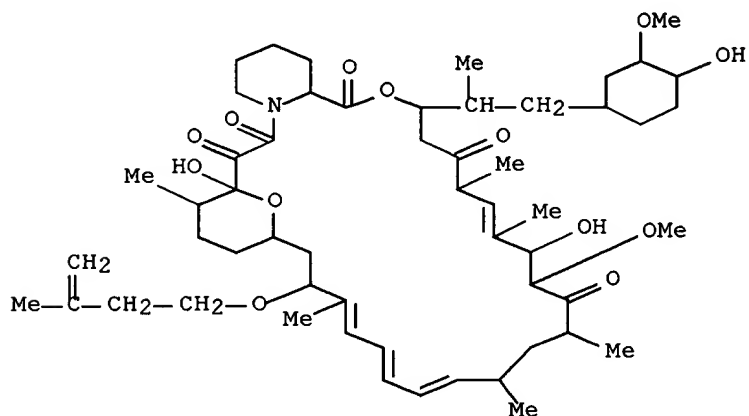


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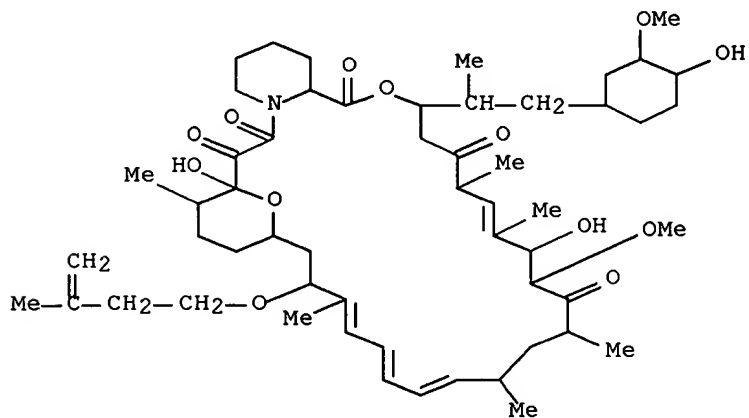
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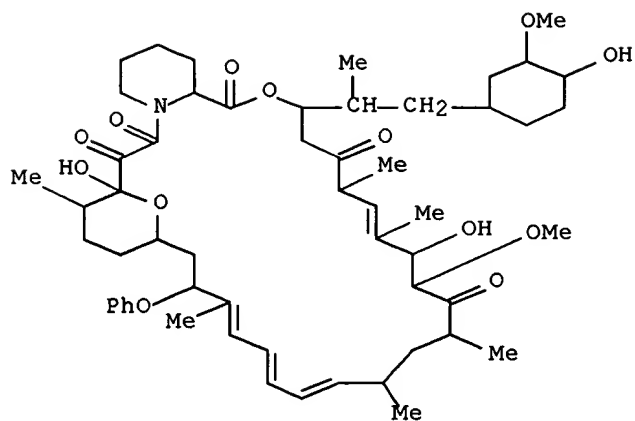
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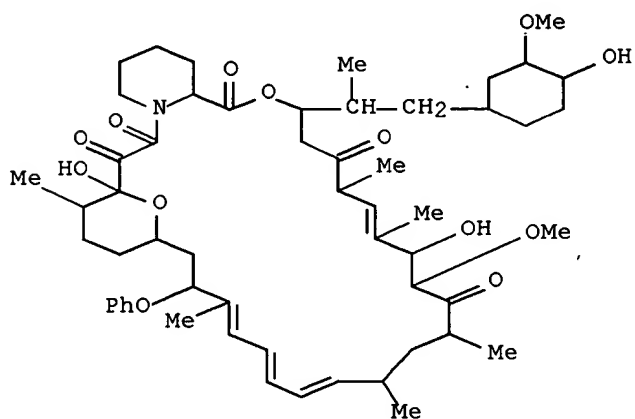
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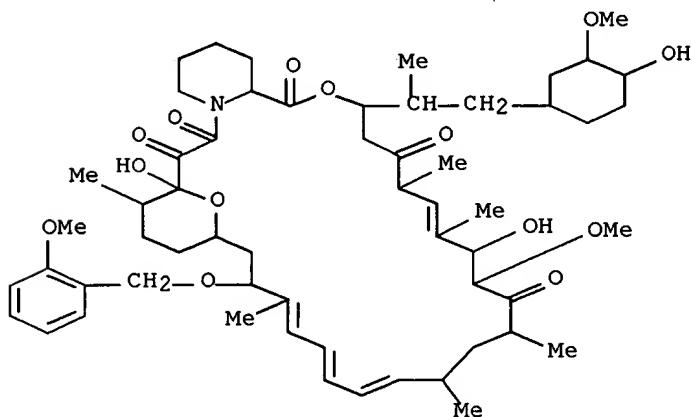
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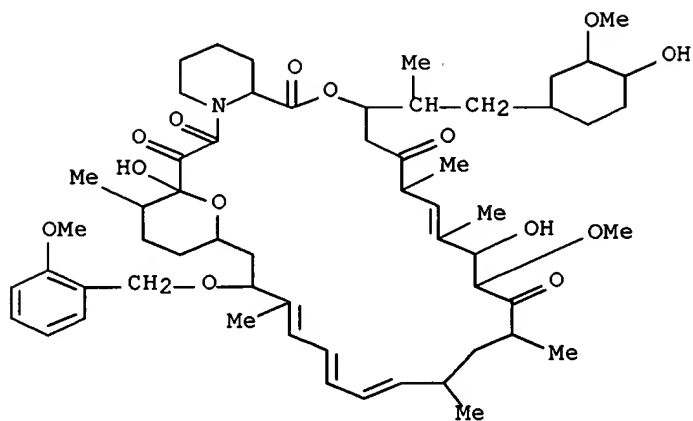
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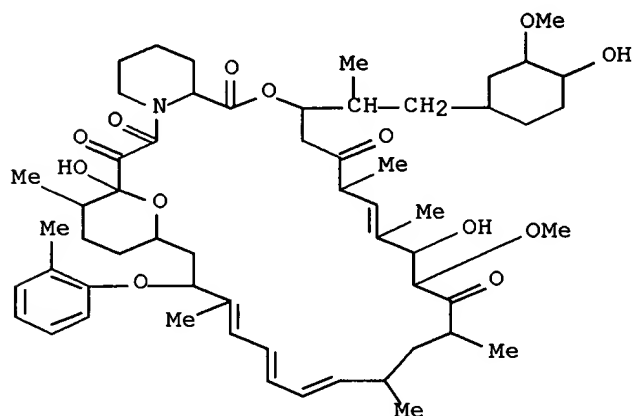


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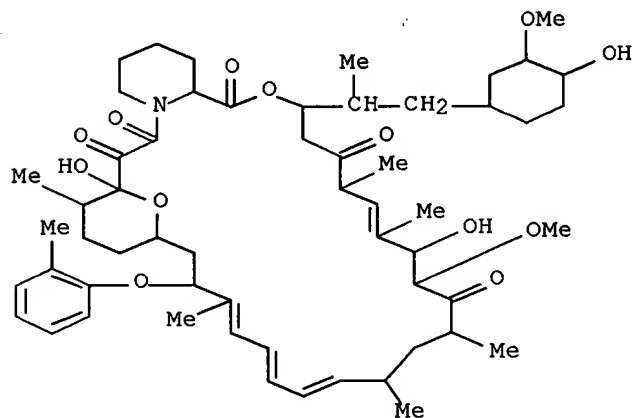
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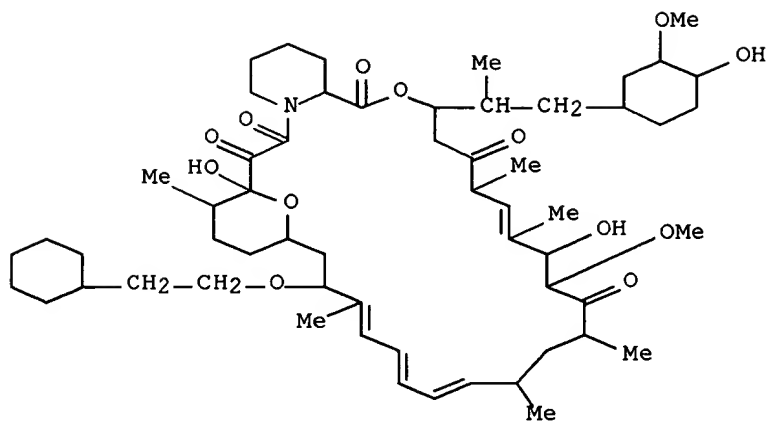
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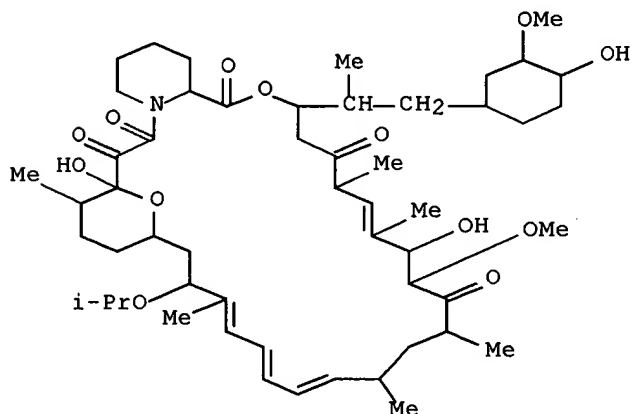
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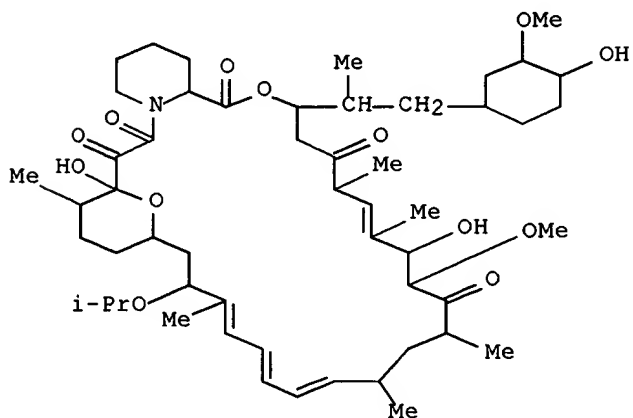
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CN Rapamycin, 7-O-demethyl-7-O-(1-methylethyl)-, (31S)- (9CI) (CA INDEX NAME)



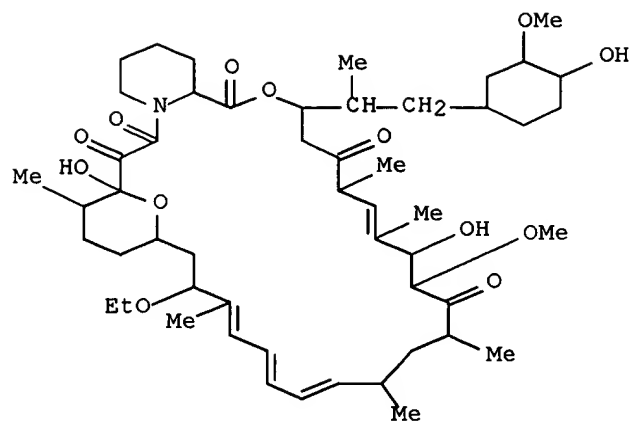
RN 328059-99-0 CAPLUS

CN Rapamycin, 7-O-demethyl-7-O-(1-methylethyl)-, (7R,31S)- (9CI) (CA INDEX NAME)



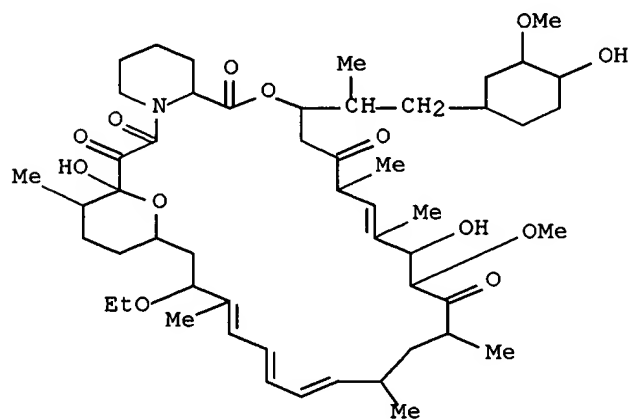
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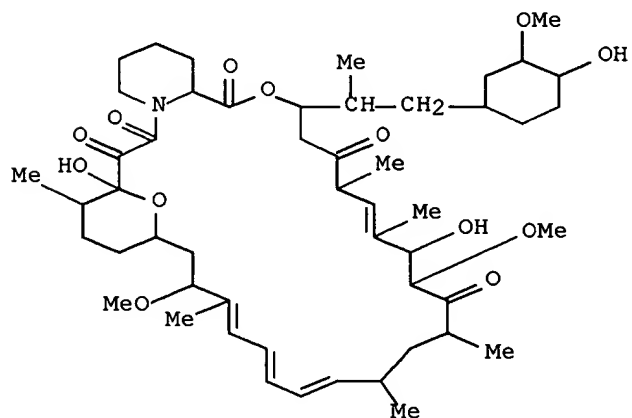
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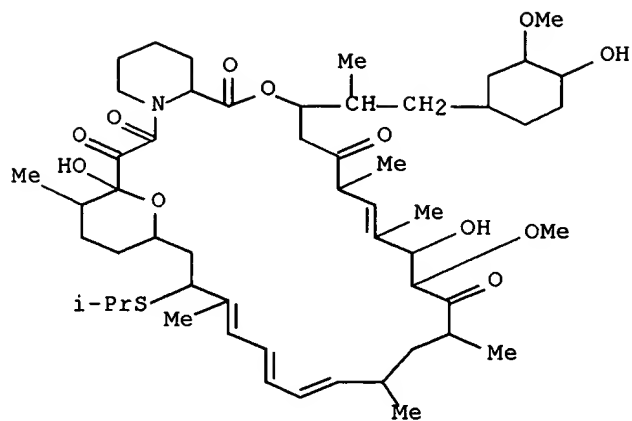
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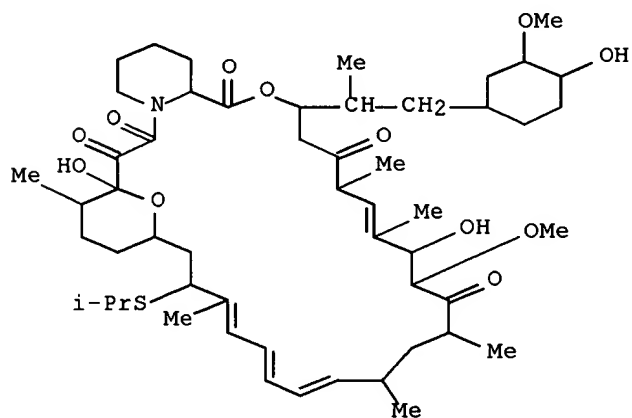


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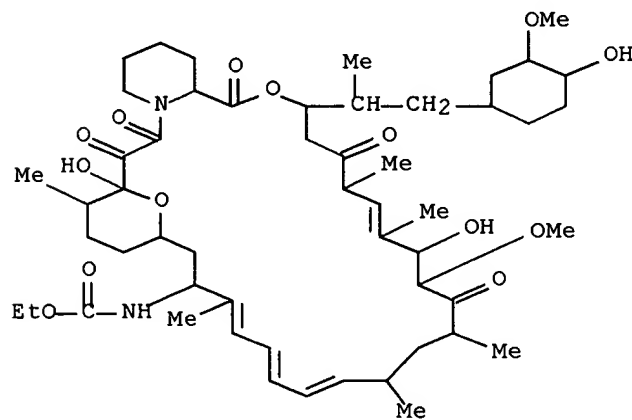
CN Rapamycin, 7-demethoxy-7-[(1-methylethyl)thio]-, (31S)- (9CI) (CA INDEX NAME)



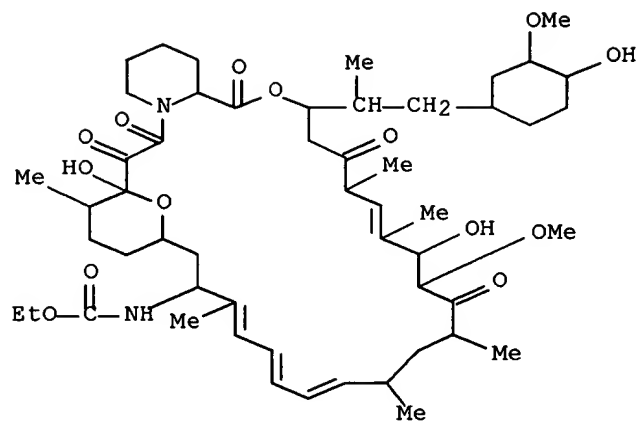
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 CN Rapamycin, 7-demethoxy-7-[(1-methylethyl)thio]-, (7R,31S)- (9CI) (CA INDEX NAME)



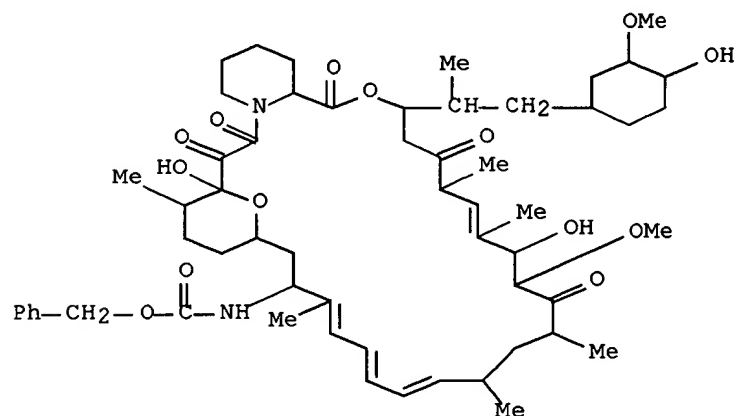
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 CN Rapamycin, 7-demethoxy-7-[(ethoxycarbonyl)amino]-, (31S)- (9CI) (CA INDEX NAME)



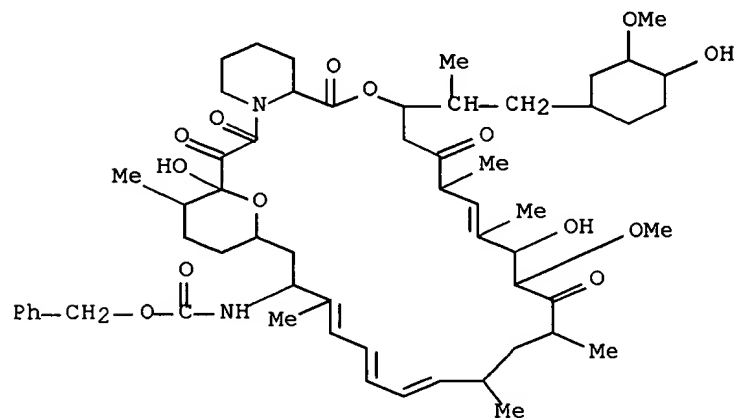
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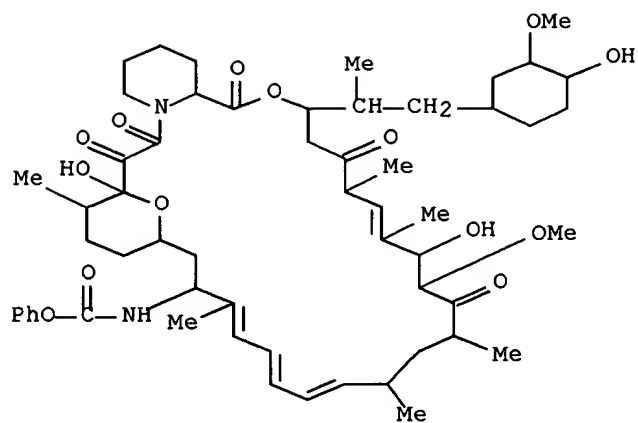
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 (CA INDEX NAME)



RN 328060-08-8 CAPLUS
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 (9CI) (CA INDEX NAME)

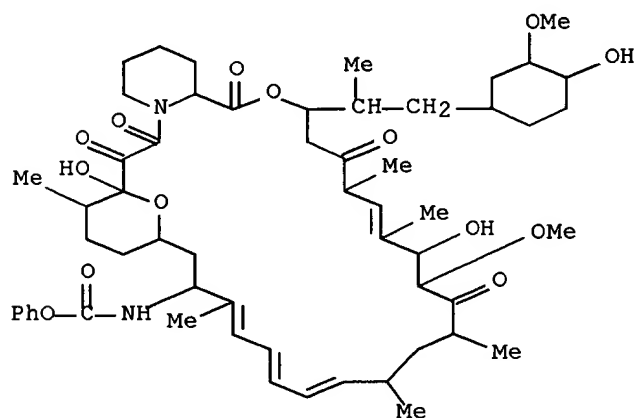


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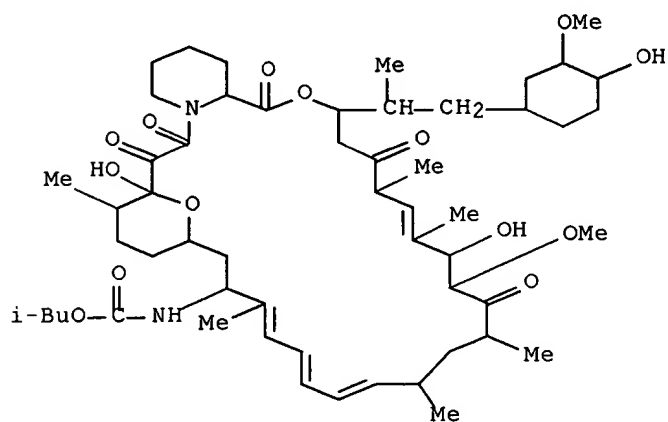
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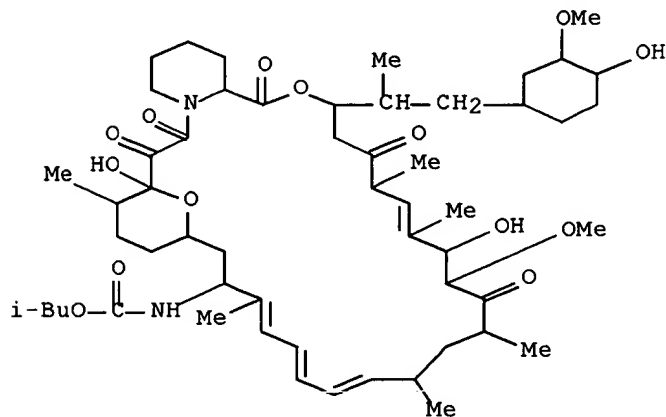


RN 328060-11-3 CAPLUS

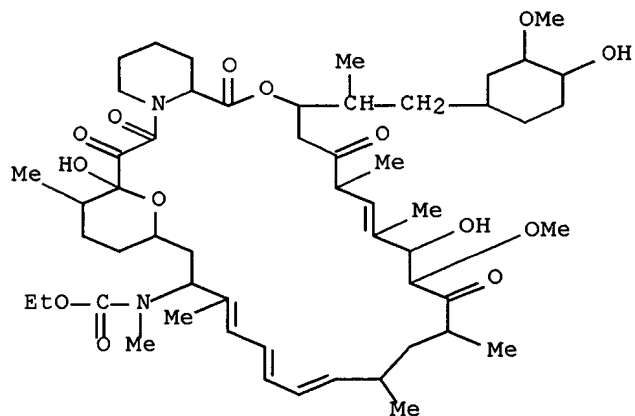
CN Rapamycin, 7-demethoxy-7-[[(2-methylpropoxy)carbonyl]amino]-, (31S)- (9CI) (CA INDEX NAME)



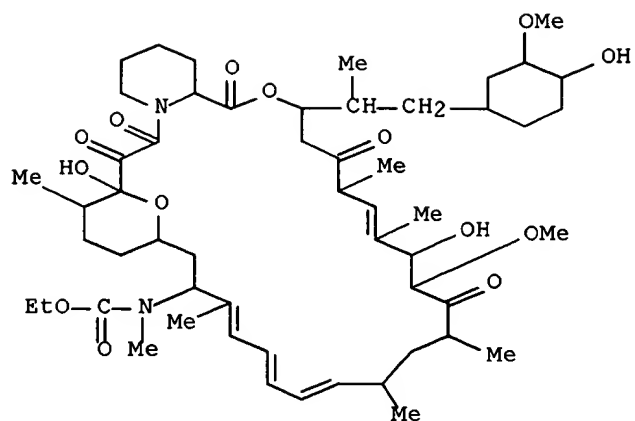
RN 328060-12-4 CAPLUS
 CN Rapamycin, 7-demethoxy-7-[[(2-methylpropoxy) carbonyl]amino]-, (7R,31S)-
 (9CI) (CA INDEX NAME)



RN 328060-13-5 CAPLUS
 CN Rapamycin, 7-demethoxy-7-[(ethoxycarbonyl)methylamino]-, (7R,31S)- (9CI)
 (CA INDEX NAME)

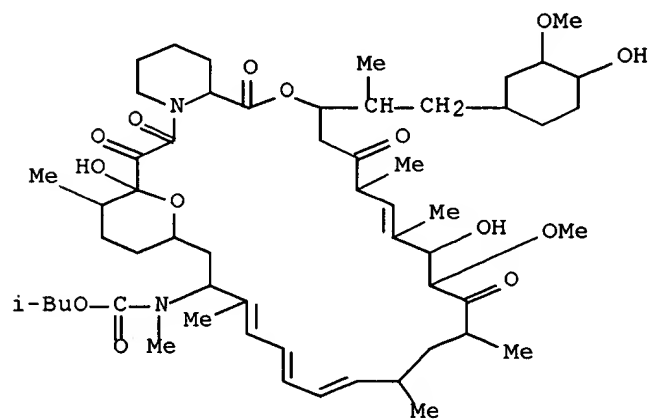


RN 328060-14-6 CAPLUS
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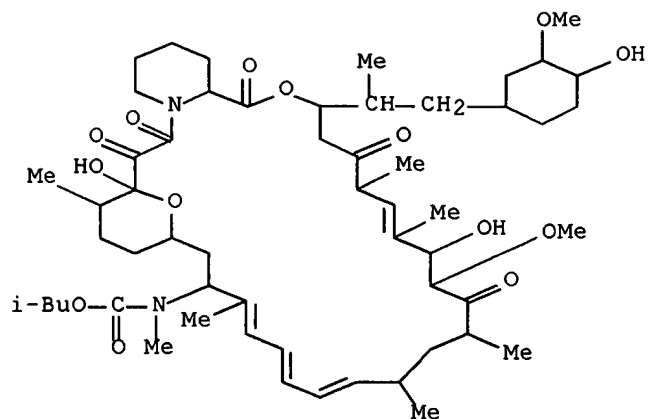
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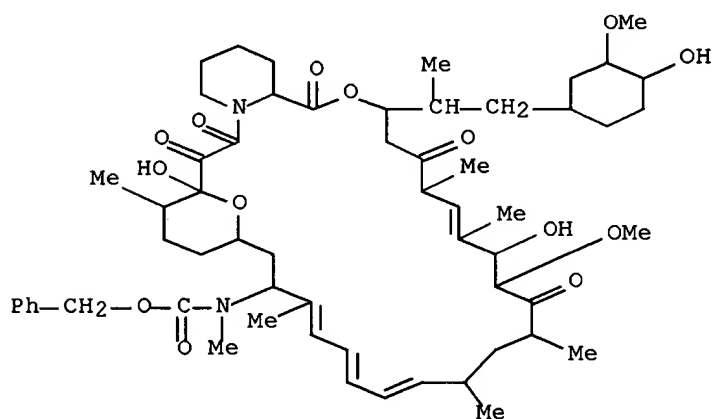
RN 328060-16-8 CAPLUS

CN Rapamycin, 7-demethoxy-7-[methyl[(2-methylpropoxy)carbonyl]amino]-,
(7R,31S)- (9CI) (CA INDEX NAME)



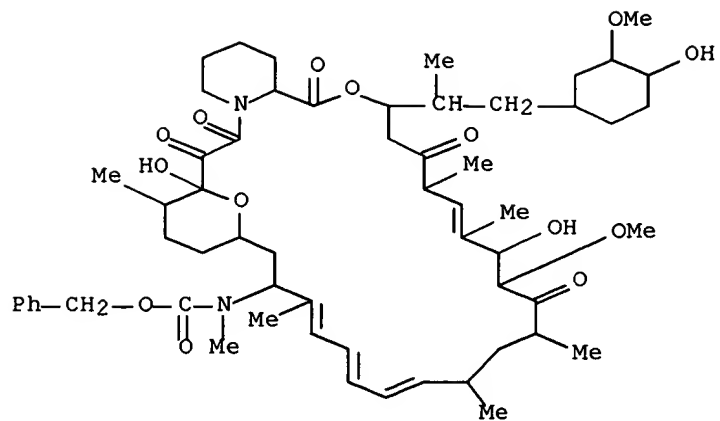
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CN Rapamycin, 7-demethoxy-7-[methyl[(phenylmethoxy)carbonyl]amino]-, (31S)-
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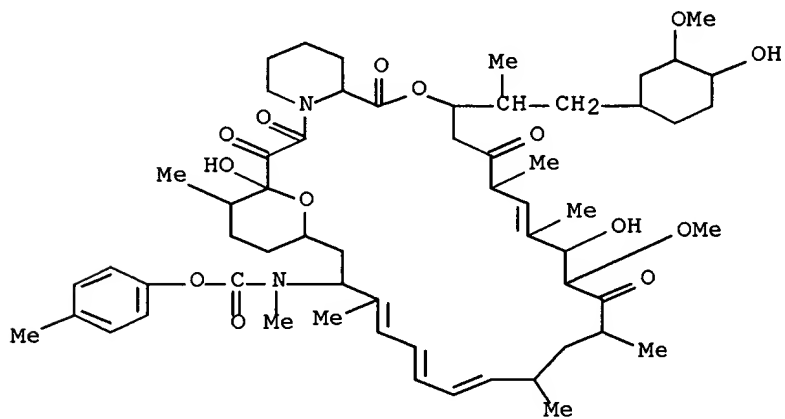
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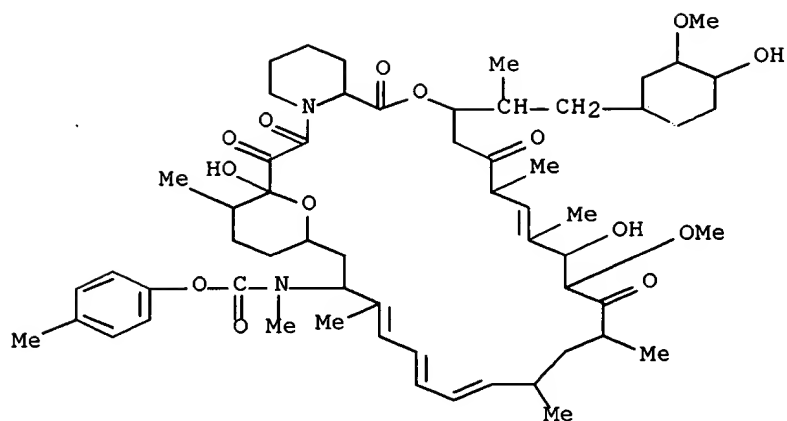
CN Rapamycin, 7-demethoxy-7-[methyl[(4-methylphenoxy)carbonyl]amino]-, (31S)-

(9CI) (CA INDEX NAME)



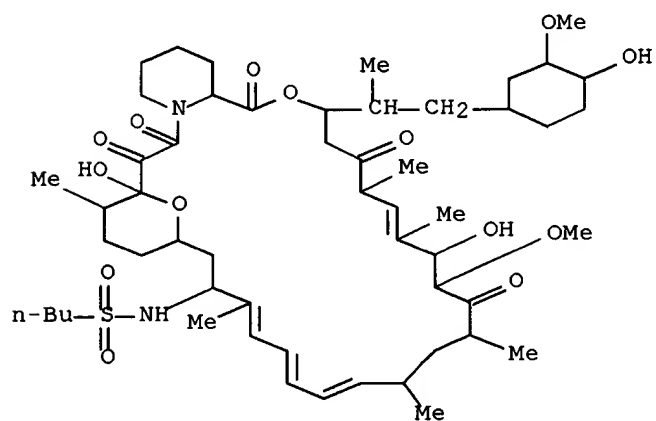
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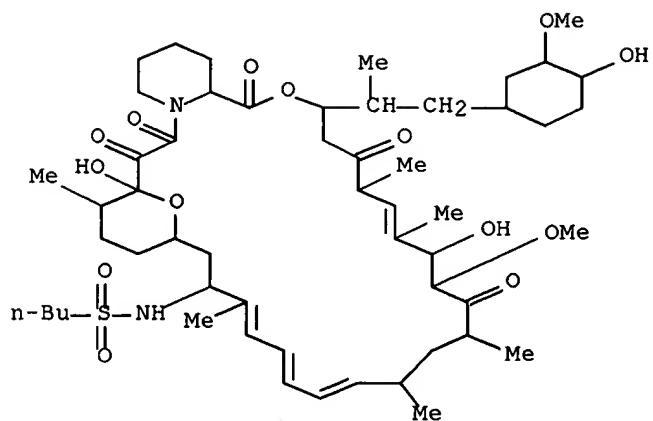
RN 328060-21-5 CAPLUS

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RN 328060-22-6 CAPLUS

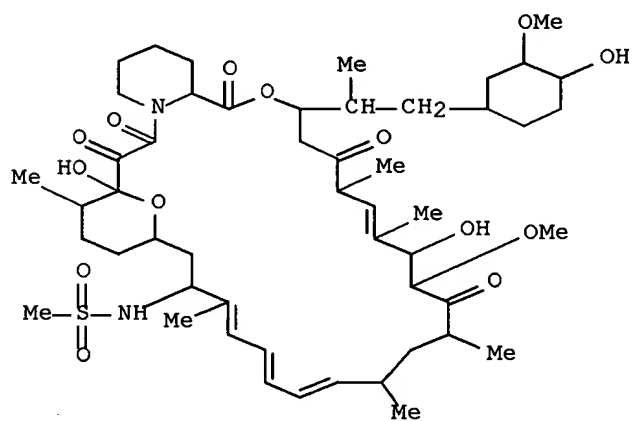
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RN 328060-23-7 CAPLUS

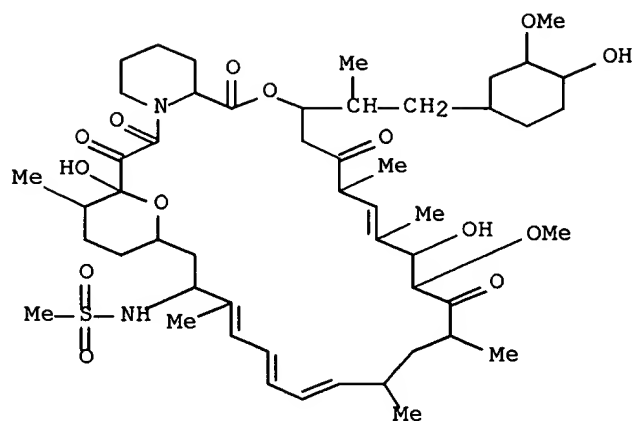
CN Rapamycin, 7-demethoxy-7-[(methanesulfonyl)amino]-, (31S)- (9CI) (CA

INDEX
NAME)



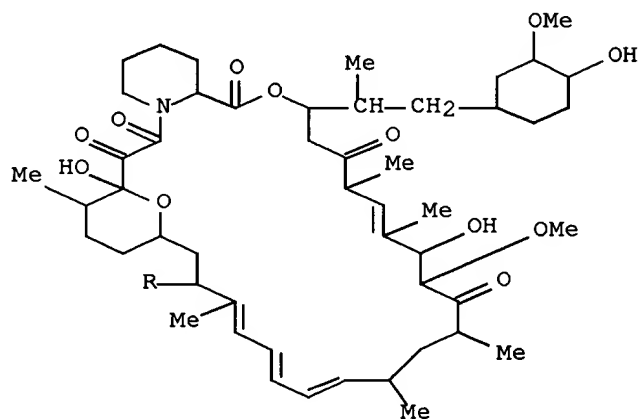
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INDEX NAME)

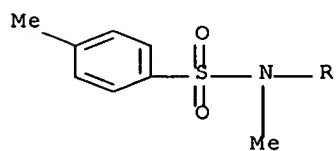


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 CN Rapamycin, 7-demethoxy-7-[methyl[(4-methylphenyl)sulfonyl]amino]-,
 (7R,31S)- (9CI) (CA INDEX NAME)

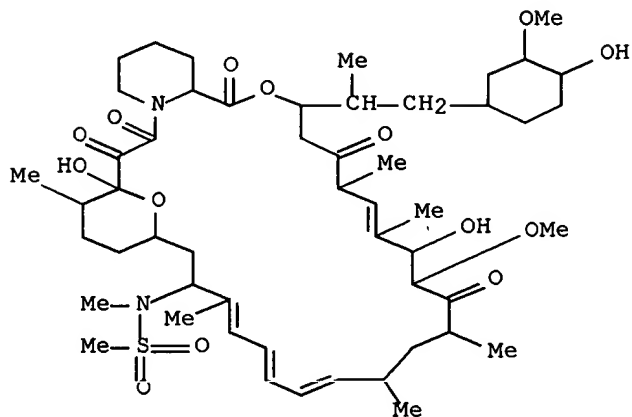
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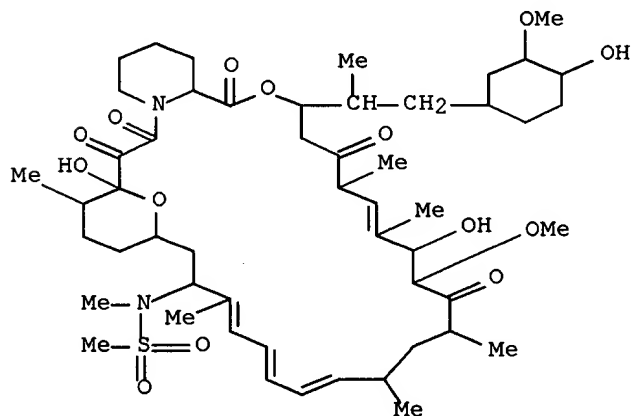
PAGE 2-A



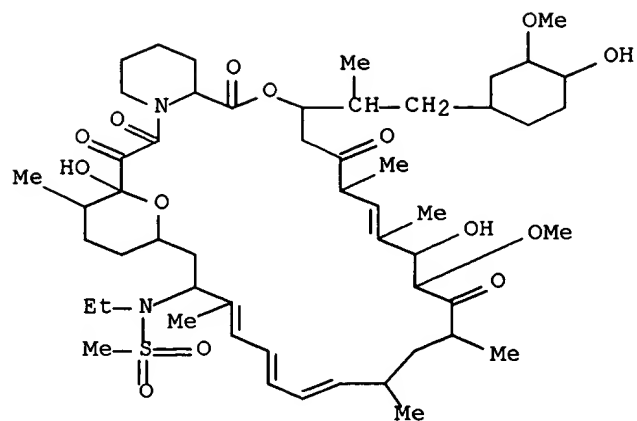
RN 328060-26-0 CAPLUS
 CN Rapamycin, 7-demethoxy-7-[methyl(methylsulfonyl)amino]-, (31S)- (9CI)
 (CA INDEX NAME)



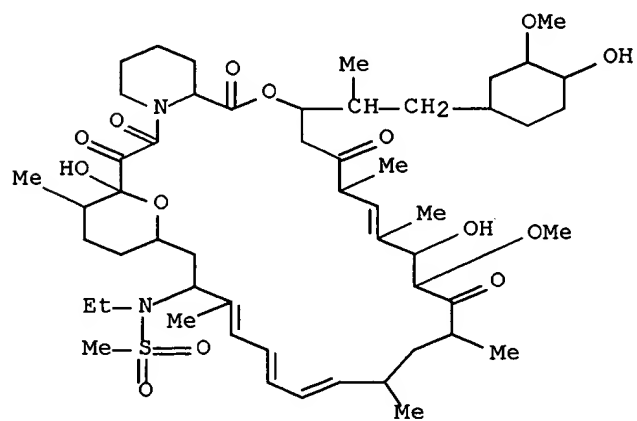
RN 328060-27-1 CAPLUS
 CN Rapamycin, 7-demethoxy-7-[methyl(methylsulfonyl)amino]-, (7R,31S)- (9CI)
 (CA INDEX NAME)



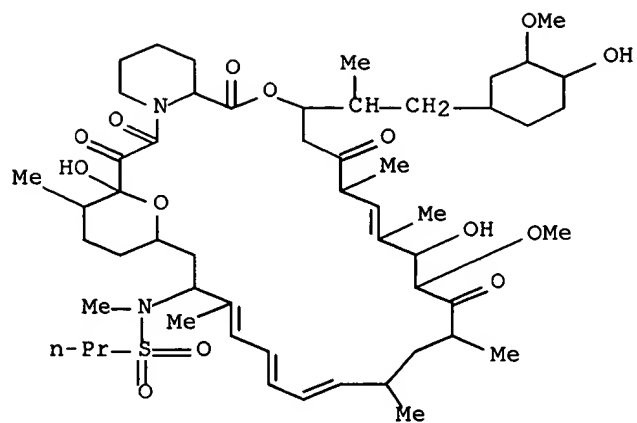
RN 328060-28-2 CAPLUS
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RN 328060-29-3 CAPLUS
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 (CA INDEX NAME)

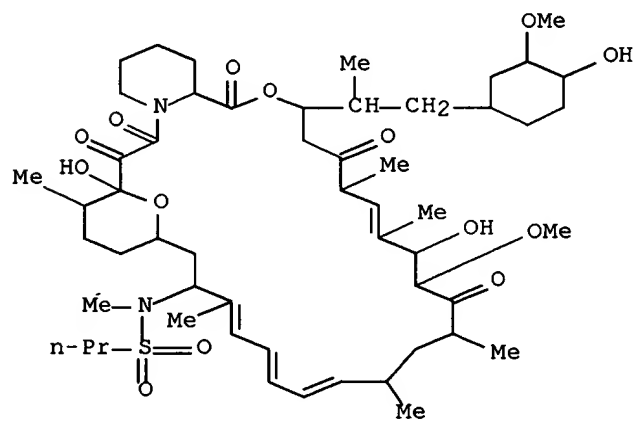


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 (CA INDEX NAME)



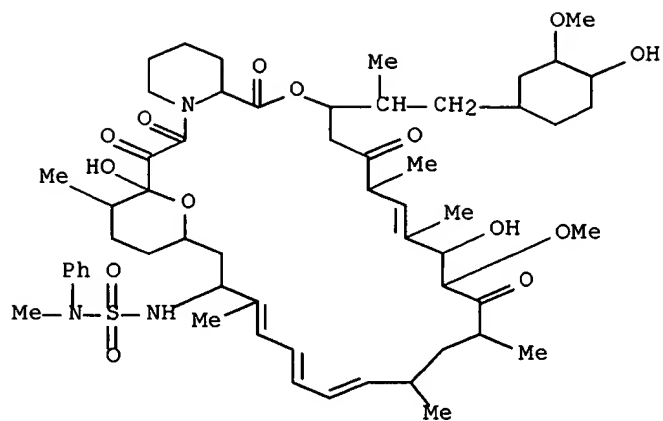
RN 328060-31-7 CAPLUS

CN Rapamycin, 7-demethoxy-7-[methyl(propylsulfonyl)amino]-, (7R,31S)- (9CI)
(CA INDEX NAME)



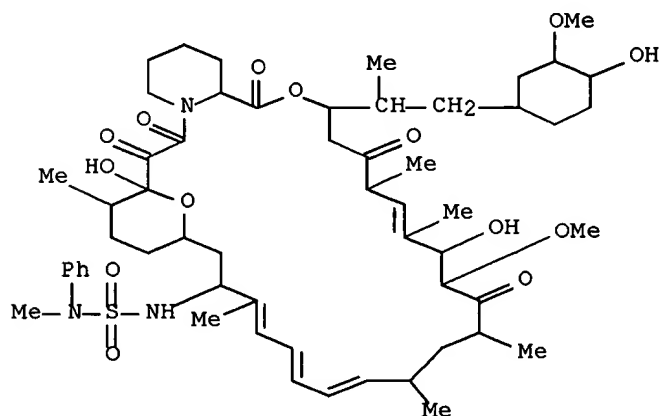
RN 328060-32-8 CAPLUS

CN Rapamycin, 7-demethoxy-7-[(methylphenylamino)sulfonyl]amino]-, (31S)-
(9CI) (CA INDEX NAME)



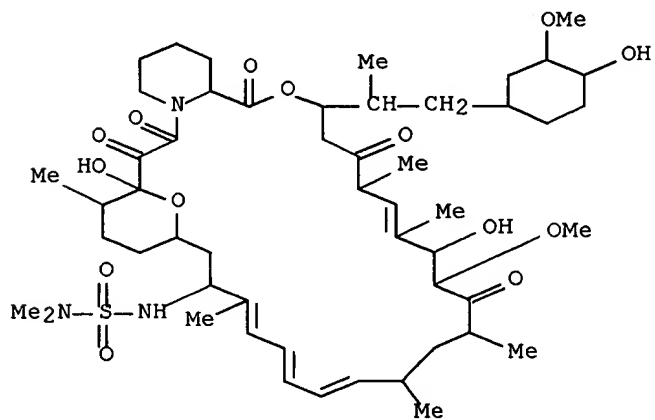
RN 328060-33-9 CAPLUS

CN Rapamycin, 7-demethoxy-7-[[[(methylphenylamino)sulfonyl]amino]-, (7R,31S)-(9CI) (CA INDEX NAME)



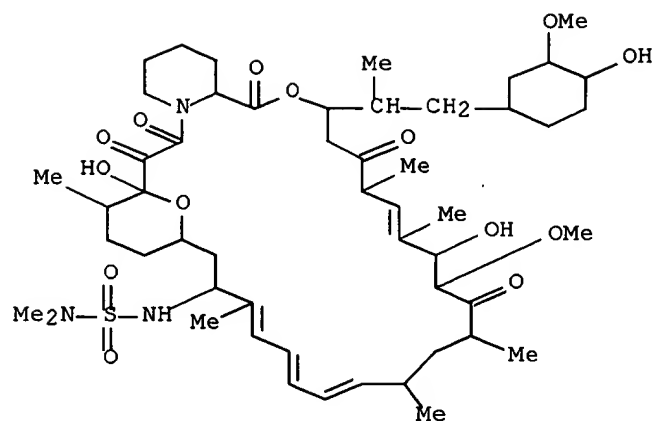
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CN Rapamycin, 7-demethoxy-7-[[[(dimethylamino)sulfonyl]amino]-, (31S)-(9CI) (CA INDEX NAME)



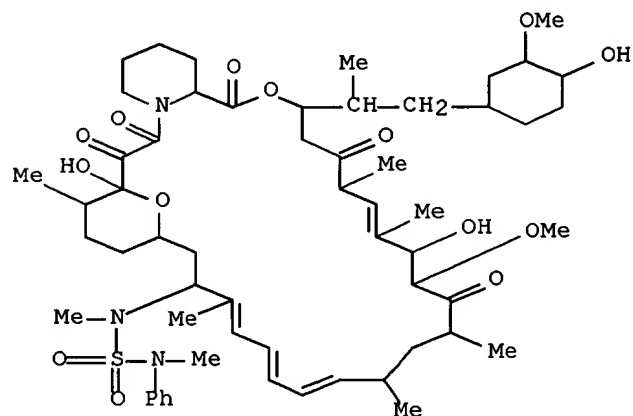
RN 328060-35-1 CAPLUS

CN Rapamycin, 7-demethoxy-7-[[[(dimethylamino)sulfonyl]amino]-, (7R,31S)-(9CI) (CA INDEX NAME)



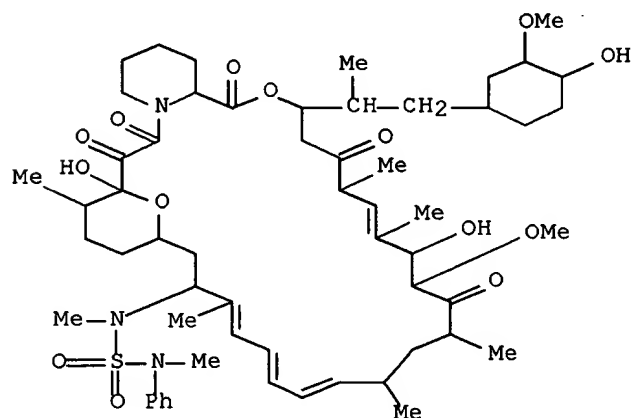
RN 328060-36-2 CAPLUS

CN Rapamycin, 7-demethoxy-7-[methyl[(methylphenylamino)sulfonyl]amino]-,
(31S)- (9CI) (CA INDEX NAME)



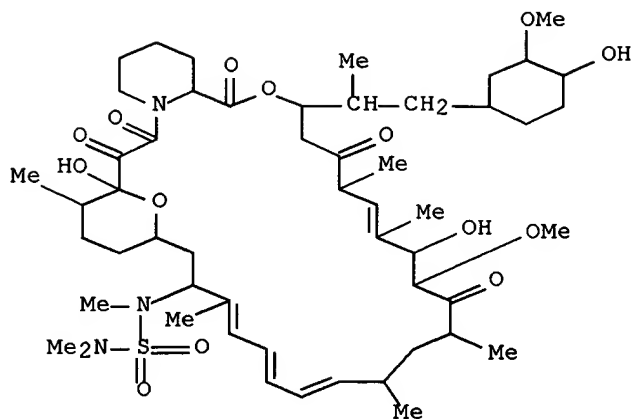
RN 328060-37-3 CAPLUS

CN Rapamycin, 7-demethoxy-7-[methyl[(methylphenylamino)sulfonyl]amino]-,
(7R,31S)- (9CI) (CA INDEX NAME)



RN 328060-38-4 CAPLUS

CN Rapamycin, 7-demethoxy-7-[[dimethylamino)sulfonyl]methylamino]-,
(7R,31S)- (9CI) (CA INDEX NAME)



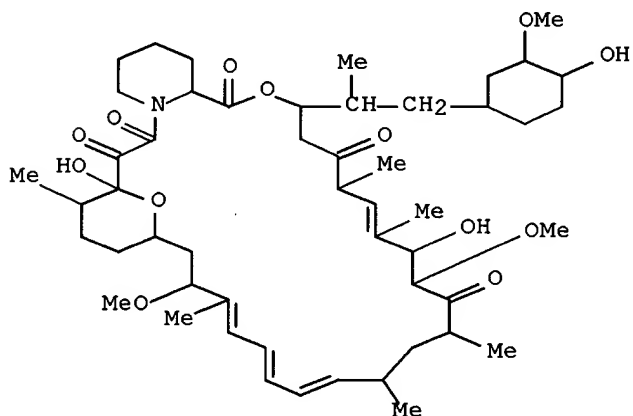
IT **253431-35-5P**, 28-Epirapamycin

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(tautomer; synthesis and biol. activity of 28-epirapalogs with reduced immunosuppressive activity for multimerizing chimeric proteins)

RN 253431-35-5 CAPLUS

CN Rapamycin, (31S)- (9CI) (CA INDEX NAME)



RE.CNT 8

RE

(1) American Home Products Corp; WO 9809972 A 1998 CAPLUS

(2) Ariad Gene Therapeutics; WO 9641865 A 1996 CAPLUS

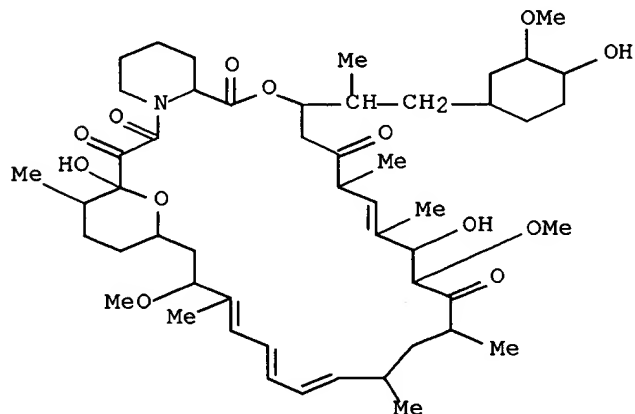
(3) Ariad Gene Therapeutics; WO 9936553 A 1999 CAPLUS

(4) Hayward, C; Journal of the American Chemical Society 1993, V115(20), P9345 CAPLUS

(5) Mahrwald, R; Synthesis 1990, 7, P592 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2001 ACS
 AN 1999:757399 CAPLUS
 DN 132:64087
 TI Selective Epimerization of Rapamycin via a Retroaldol/Aldol Mechanism Mediated by Titanium Tetraisopropoxide
 AU Yang, Wu; Digits, Cheryl A.; Hatada, Marcos; Narula, Surinder; Rozamus, Leonard W.; Huestis, Cameran M.; Wong, Jason; Dalgarno, David; Holt, Dennis A.
 CS ARIAD Gene Therapeutics Inc., Cambridge, MA, 02139-4234, USA
 SO Org. Lett. (1999), 1(12), 2033-2035
 CODEN: ORLEF7; ISSN: 1523-7060
 PB American Chemical Society
 DT Journal
 LA English
 AB The efficient and selective epimerization of the immunosuppressant rapamycin to 28-epirapamycin under mild conditions is described. The mechanism of epimerization involves an equil. of the four C28/C29 diastereomers through a two-step retroaldol/aldol (macrocycle ring-opening/ring-closing) sequence. This retroaldol/aldol equilibration is not restricted to rapamycin but is also applicable to acyclic .beta.-hydroxyketones. A potentially useful extension of this method-the use of .beta.-hydroxyketones as enolate synthons for effecting inter- or intramol. aldol reactions under neutral conditions-is demonstrated.
 IT 253431-35-5P, 28-Epirapamycin
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (selective epimerization of rapamycin via a retroaldol/aldol mechanism mediated by titanium tetraisopropoxide)
 RN 253431-35-5 CAPLUS
 CN Rapamycin, (31S)- (9CI) (CA INDEX NAME)



RE.CNT 16

RE

- (1) Findlay, J; Can J Chem 1980, V58, P579 CAPLUS
 - (2) Hayward, C; J Am Chem Soc 1993, V115, P9345 CAPLUS
 - (4) Heathcock, C; J Org Chem 1980, V45, P1066 CAPLUS
 - (5) House, H; J Am Chem Soc 1973, V95, P3310 CAPLUS
 - (6) Hughes, P; Tetrahedron Lett 1992, V33, P4739 CAPLUS
- ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2001 ACS

AN 1998:175931 CAPLUS

DN 128:230188

TI synthesis and biological activity of rapamycin derivatives with unnatural stereochemistries

IN Grinfield, Alexander Alesksey; Hu, David Cheng; Caufield, Craig Eugene

PA American Home Products Corporation, USA

SO PCT Int. Appl., 37 pp.

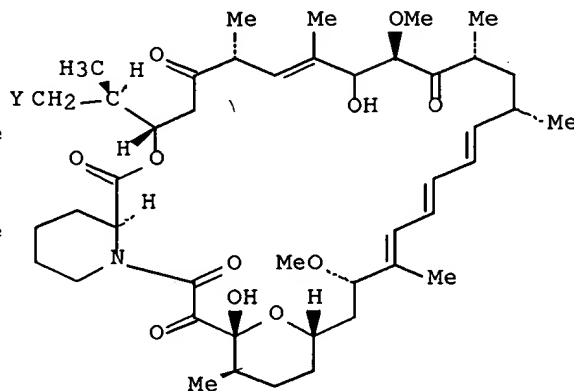
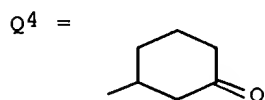
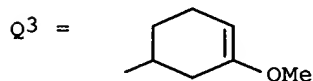
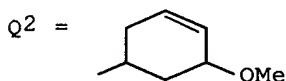
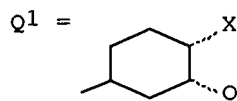
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

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	RW:	GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			
	AU 9742461	A1	19980326	AU 1997-42461	19970902
PRAI	US 1996-709318		19960909		
	WO 1997-US15438		19970902		
OS	MARPAT 128:230188				
GI					



I

AB Rapamycin derivs. (I) [Y = Q1, Q2, Q3, Q4; X = OH, -OR1, -SO2Ar, -SO2R1, N3, -OAr, -NH(C=O)Ar, -NH(C=O)R1, -NH(C=O)NR2R3, -NHCN, I, Cl, F, Br, -SCN, or 1,2,3-triazole optionally substituted with methoxycarbonyl; R1 = alkyl, cycloalkyl, (CH2)1-10NHR2, piperdiny1, pyrrolidinyl, piperazinyl, (CH2)1-10Ar, CH2CH(OR4)CH2OR5, CH2-1,2:3,4-diisopropylidenegalactose; R2, R3 = alkyl, Ar, H, (CH2)1-10Ar; R4, R5 = H, alkyl, (CH2)1-10Ar, together form isopropylidne; Ar = Ph, naphthyl, pyridyl, quinolyl, indolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, and may be substituted with F, Cl, Br, I, NO2, OH, alkyl, alkoxy, CH2OH, 3,4-methylenedioxy] are prepd. as well as pharmaceutically acceptable salts when one can be formed. Is possess immunosuppressive and/or anti-tumor and/or antiinflammatory activity in vivo and/or inhibit thymocyte proliferation in vitro and are, therefore, useful in the treatment of transplantation rejection, autoimmune diseases such as lupus, rheumatoid arthritis,

diabetes mellitus, multiple sclerosis and in the treatment of *Candida albicans* infections and also in treatment of diseases of inflammation..

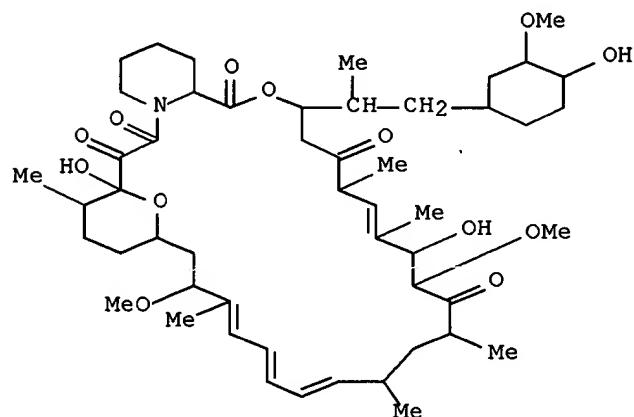
IT **204635-42-7P**, 31,42-epi-Rapamycin

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(synthesis and biol. activity of rapamycin derivs. with unnatural stereochemistries)

RN 204635-42-7 CAPLUS

CN Rapamycin, (31S,42S)- (9CI) (CA INDEX NAME)

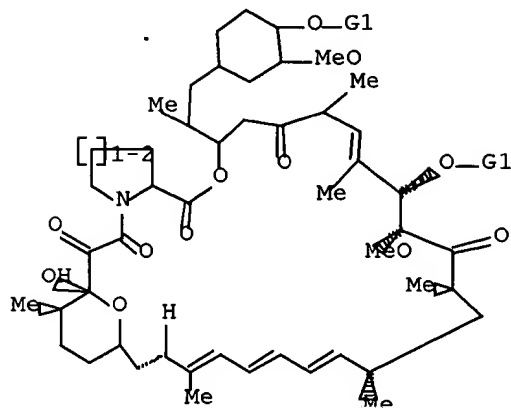


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L38 HAS NO ANSWERS

L36 SCR 1821 OR 1822 OR 1823 OR 1824

L37 STR



G1 H, Ak

Structure attributes must be viewed using STN Express query preparation.

L38 QUE ABB=ON PLU=ON L37 AND L36 AND L36

(FILE 'HOME' ENTERED AT 18:15:15 ON 12 APR 2001)

FILE 'REGISTRY' ENTERED AT 18:15:48 ON 12 APR 2001

L1 SCREEN 1821 OR 1822 OR 1823 OR 1824

L2 STRUCTURE UPLOADED

L3 QUE L2 AND L1 AND L1

L4 34 S L3

L5 695 S L3 FUL

FILE 'STNGUIDE' ENTERED AT 18:16:57 ON 12 APR 2001

FILE 'REGISTRY' ENTERED AT 18:18:32 ON 12 APR 2001

L6 SCREEN 1821 OR 1822 OR 1823 OR 1824

L7 STRUCTURE UPLOADED

L8 QUE L7 AND L6 AND L6

L9 32 S L8 SAM SUB=L5

L10 624 S L8 FUL SUB=L5

L11 SCREEN 1821 OR 1822 OR 1823 OR 1824

L12 STRUCTURE UPLOADED

L13 QUE L12 AND L11 AND L11

L14 0 S L13 SAM SUB=L5

L15 2 S L13 FUL SUB=L5

FILE 'CAPLUS' ENTERED AT 18:21:17 ON 12 APR 2001

L16 4 S L15

FILE 'STNGUIDE' ENTERED AT 18:22:25 ON 12 APR 2001

FILE 'REGISTRY' ENTERED AT 18:30:31 ON 12 APR 2001

L17 SCREEN 1821 OR 1822 OR 1823 OR 1824

L18 STRUCTURE UPLOADED

L19 QUE L18 AND L17 AND L17

L20 32 S L19 SAM SUB=L5

L21 624 S L19 FUL SUB=L5

FILE 'CAPLUS' ENTERED AT 18:32:38 ON 12 APR 2001
 L22 1388 S L21
 L23 1388 S L5

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 FILE 'REGISTRY' ENTERED AT 18:37:26 ON 12 APR 2001
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 L25 STRUCTURE UPLOADED
 L26 QUE L25 AND L24 AND L24
 L27 1 S L26 SAM SUB=L5
 L28 25 S L26 FUL SUB=L5

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 L29 4 S L28

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 FILE 'STNGUIDE' ENTERED AT 18:47:46 ON 12 APR 2001

 FILE 'REGISTRY' ENTERED AT 19:04:28 ON 12 APR 2001
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 L31 STRUCTURE UPLOADED
 L32 QUE L31 AND L30 AND L30
 L33 30 S L32 SAM SUB=L5
 L34 635 S L32 FUL SUB=L5

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 L35 1388 S L34

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 FILE 'REGISTRY' ENTERED AT 19:14:00 ON 12 APR 2001
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 L37 STRUCTURE UPLOADED
 L38 QUE L37 AND L36 AND L36
 L39 1 S L38
 L40 65 S L38 FUL

 FILE 'CAPLUS' ENTERED AT 19:14:48 ON 12 APR 2001
 L41 3 S L40

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FULL ESTIMATED COST	13.22	817.90
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
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CA SUBSCRIBER PRICE	-1.76	-28.80
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Connection closed by remote host		

L29 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2001 ACS
 AN 2001:111506 CAPLUS
 DN 134:173056
 TI Regulation of biol. events using novel compds. comprizing chimeric proteins containing FKBP and FRB domains and rapamycin analogs lacking immunosuppressive action
 IN Clarkson, Timothy P.; Gilman, Michael Z.; Holt, Dennis A.; Keenan, Terence P.; Rozamus, Leonard; Yang, Wu
 PA Ariad Pharmaceuticals, Inc., USA
 SO U.S., 101 pp., Cont.-in-part of U.S. Ser. No. 791,044, abandoned.
 CODEN: USXXAM
 DT Patent
 LA English
 FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6187757	B1	20010213	US 1998-12097	19980122
	WO 9641865	A1	19961227	WO 1996-US9948	19960607
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	RW:				
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	WO 9936553	A2	19990722	WO 1999-US178	19990115
	WO 9936553	A3	19991021		
	W:				
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	AU 9922132	A1	19990802	AU 1999-22132	19990115
	EP 1045915	A2	20001025	EP 1999-902059	19990115
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PRAI	US 1995-481941		19950607		
	US 1996-15502		19960209		
	WO 1996-US9948		19960607		
	US 1997-791044		19970128		
	US 1996-598776		19960209		
	US 1998-71591		19980115		
	US 1998-72016		19980121		
	US 1998-12097		19980122		
	US 1998-72219		19980122		
	WO 1999-US178		19990115		
OS	MARPAT 134:173056				
AB	Materials and methods are disclosed for regulation of biol. events such as target gene transcription and growth, proliferation or differentiation of engineered cells. This invention provides methods and materials for multimerizing chimeric proteins in genetically engineered cells using improved rapamycin analogs (rapalogs), preferably while avoiding the immunosuppressive effects of rapamycin. The genetically engineered cells contain one or more recombinant nucleic acid constructs encoding specialized chimeric proteins as described herein. Typically a first chimeric protein contains one or more FKBP domains which are capable of binding to an improved rapalog of this invention. This first chimeric protein is also referred to herein as an "FKBP fusion protein" and				

further comprises at least one protein domain heterologous to at least one of its FKBP domains. The complex formed by the binding of the FKBP fusion protein to the rapalog is capable of binding to a second chimeric protein which contains one or more FRB domains (the "FRB fusion protein"). The FRB fusion protein further comprises at least one protein domain heterologous to at least one of its FRB domains. In some embodiments, the FKBP fusion protein and the FRB fusion protein are different from one another. In other embodiments, however, the FKBP fusion protein is also an FRB fusion protein. In those embodiments, the chimeric protein comprises one or more FKBP domains as well as one or more FRB domains. In such cases, the first and second chimeric proteins may be the same protein, may be referred to as FKBP-FRB fusion proteins and contain at least one domain heterologous to the FKBP and/or FRB domains. The chimeric proteins may be readily designed, based on incorporation of appropriately chosen heterologous domains, such that their multimerization triggers one or more of a wide variety of desired biol. responses. The nature of the biol. response triggered by rapalog-mediated complexation is detd. by the choice of heterologous domains in the fusion proteins. The heterologous domains are therefore referred to as "action" or "effector" domains. The genetically engineered cells for use in practicing this invention will contain one or more recombinant nucleic acid constructs encoding the chimeric proteins, and in certain applications, will further contain one or more accessory nucleic acid constructs, such as one or more target gene constructs.

IT **158472-50-5P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(regulation of biol. events using chimeric proteins contg. FKBP and
FRB domains and rapamycin analogs lacking immunosuppressive action)

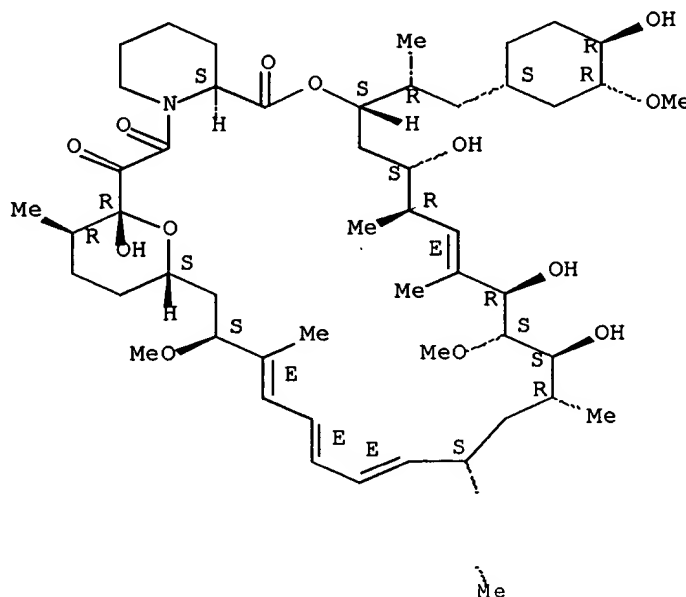
RN 158472-50-5 CAPLUS

CN Rapamycin, 27,33-dideoxo-27,33-dihydroxy-, (27S,33S)- (9CI) (CA INDEX
NAME)

Absolute stereochemistry.

Double bond geometry as shown.

PAGE 1-A

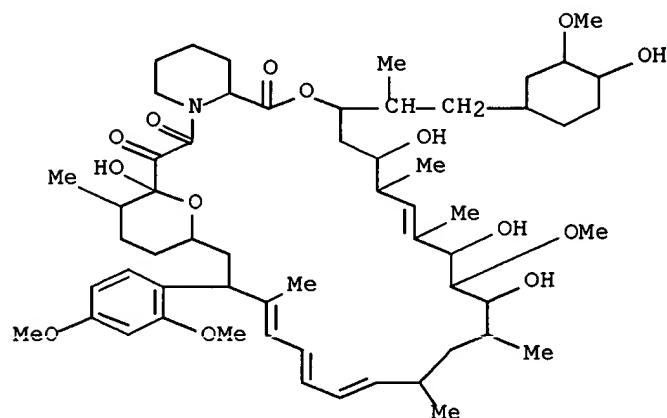


PAGE 2-A

IT **202522-60-9P**

RL: SPN (Synthetic preparation); PREP (Preparation)

FRB



RE.CNT 138

RE

- | | | | | |
|-----|----------|---------|------|--------|
| (1) | Anon; WO | 9113889 | 1991 | CAPLUS |
| (2) | Anon; WO | 9205179 | 1992 | CAPLUS |
| (3) | Anon; WO | 9214737 | 1992 | CAPLUS |
| (4) | Anon; WO | 9219595 | 1992 | CAPLUS |
| (5) | Anon; WO | 9304680 | 1993 | CAPLUS |

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2001 ACS

AN 1999:468639 CAPLUS

DN 131:112371

TI Regulation of biological events using fusion proteins of rapamycin-binding proteins and rapamycin analogs

IN Clackson, Timothy P.; Gilman, Michael Z.; Holt, Dennis A.; Keenan, Terence P.; Rozamus, Leonard; Yang, Wu

PA Ariad Gene Therapeutics, Inc., USA

SO PCT Int. Appl., 155 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9936553	A2	19990722	WO 1999-US178	19990115
	WO 9936553	A3	19991021		
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 6187757	B1	20010213	US 1998-12097	19980122
	AU 9922132	A1	19990802	AU 1999-22132	19990115
	EP 1045915	A2	20001025	EP 1999-902059	19990115
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRAI US 1998-71591 19980115
US 1998-72016 19980121
US 1998-12097 19980122
US 1998-72219 19980122
US 1995-481941 19950607
US 1996-15502 19960209
WO 1996-US9948 19960607
US 1997-791044 19970128
WO 1999-US178 19990115

OS MARPAT 131:112371

AB A method of regulating biol. processes using fusion proteins of FK506-binding proteins and regulatory protein is described. The method uses analogs of rapamycin to mediate the interaction between FK506-

binding

domains of fusion proteins. The method avoids the problems assocd. with immunosuppression by rapamycins. A series of analogs of rapamycin with substitutions at C7, C24, or C30 were prepd. and tested for their binding to FKBP. Several series of fusion proteins contg. FK506-binding domains and the DNA-binding or transcription-activating domains of a no. of well characterized transcription factors (including GAL4, VP16, NF.kappa.B p65 subunit) were prepd. by std. methods. Fusion proteins that could be activated by added rapamycin analogs were identified. Induction ratios

of

>104 were obtained. The use of these fusion proteins to direct expression

of a human growth hormone gene in mice inoculated with cells carrying a rapamycin regulated expression system was demonstrated. Phage display libraries for use in optimization of rapamycin binding and responsiveness are described. Methods of using these fusion proteins to modulate receptor-dependent processes, esp. signal transduction, are described.

IT 158472-50-5P 202522-60-9P 232591-87-6P
 232591-88-7P 232591-89-8P 232591-90-1P
 232591-91-2P 232591-92-3P 232591-93-4P
 232591-94-5P 232591-96-7P 232591-97-8P
 232591-98-9P 232591-99-0P 232592-00-6P
 232592-01-7P 232592-02-8P 232592-04-0P
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 232592-11-9P

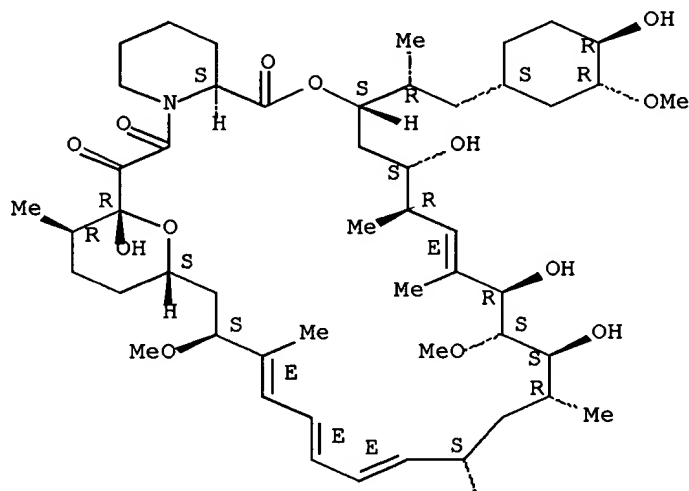
RL: BUU (Biological use, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prepn. of; regulation of biol. events using fusion proteins of rapamycin-binding proteins and rapamycin analogs)

RN 158472-50-5 CAPLUS

CN Rapamycin, 27,33-dideoxo-27,33-dihydroxy-, (27S,33S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.

PAGE 1-A

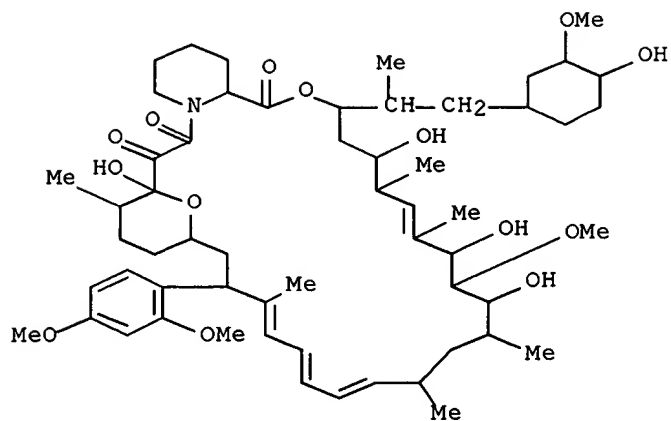


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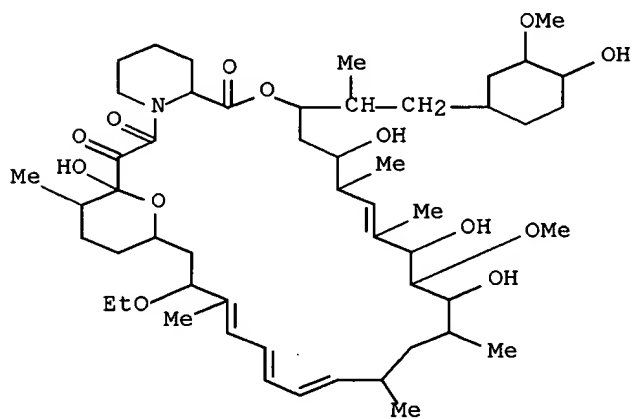
RN 202522-60-9 CAPLUS

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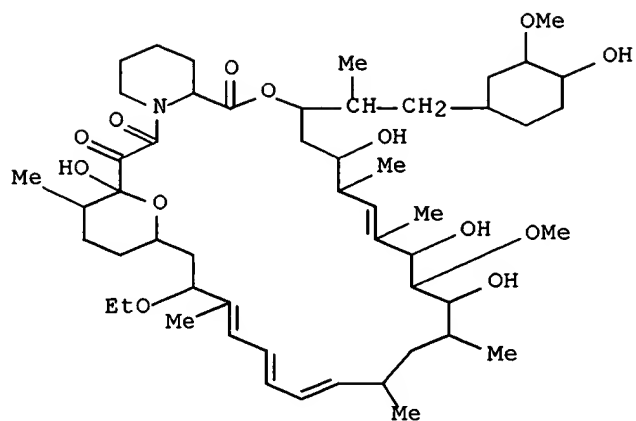
RN 232591-87-6 CAPLUS

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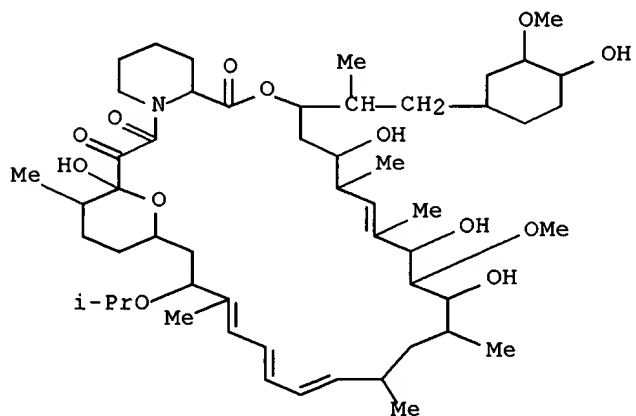


RN 232591-88-7 CAPLUS

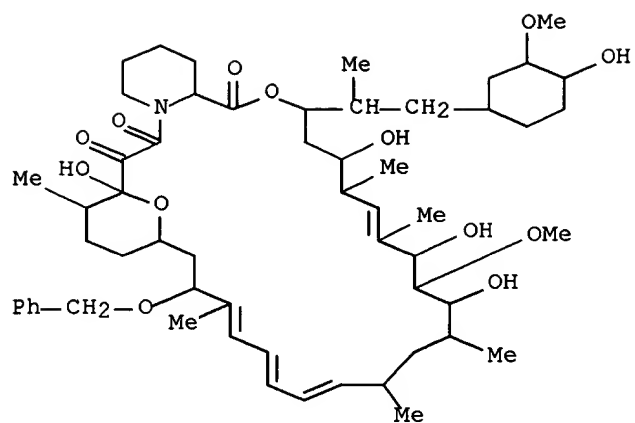
CN Rapamycin, 7-O-demethyl-27,33-dideoxo-7-O-ethyl-27,33-dihydroxy-,
(7R,27S,33S)- (9CI) (CA INDEX NAME)



RN 232591-89-8 CAPLUS
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 , (27S,33S)- (9CI) (CA INDEX NAME)

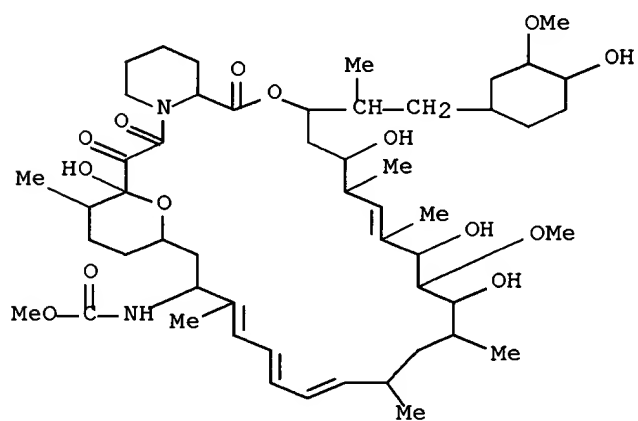


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 (CA INDEX NAME)



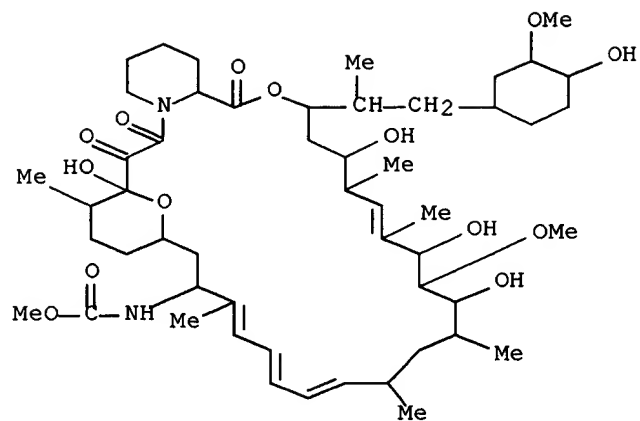
RN 232591-91-2 CAPLUS

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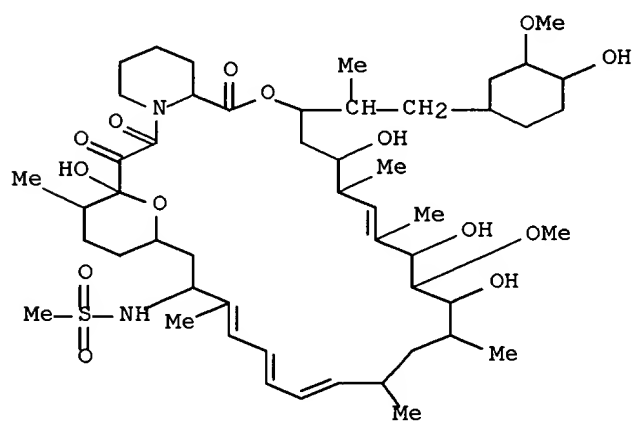
RN 232591-92-3 CAPLUS

CN Rapamycin, 7-demethoxy-27,33-dideoxo-27,33-dihydroxy-7-
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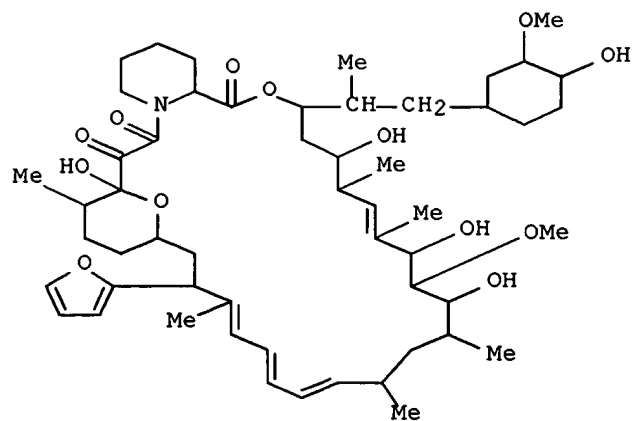
RN 232591-93-4 CAPLUS

CN Rapamycin, 7-demethoxy-27,33-dideoxo-27,33-dihydroxy-7-
[(methylsulfonyl)amino]-, (27S,33S)- (9CI) (CA INDEX NAME)



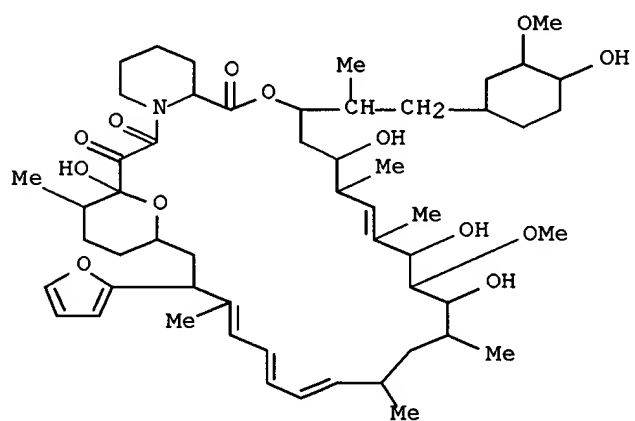
RN 232591-94-5 CAPLUS

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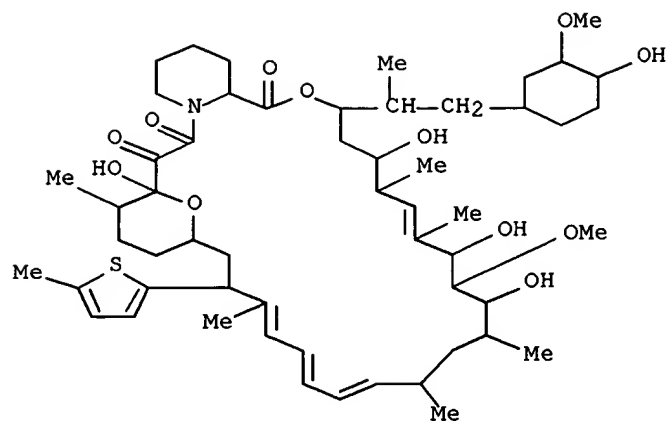
RN 232591-96-7 CAPLUS

CN Rapamycin, 7-demethoxy-27,33-dideoxo-7-(2-furanyl)-27,33-dihydroxy-, (7R,27S,33S)- (9CI) (CA INDEX NAME)



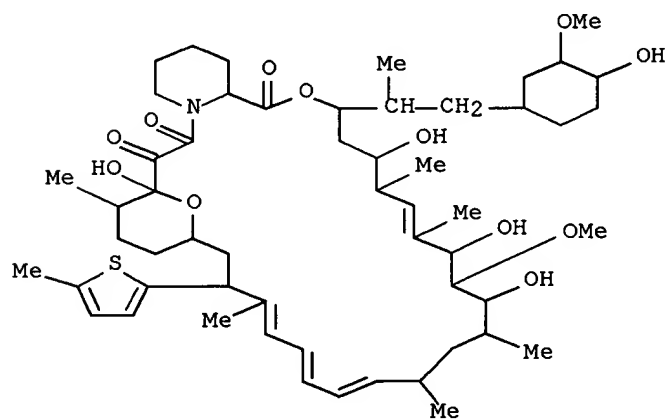
RN 232591-97-8 CAPLUS

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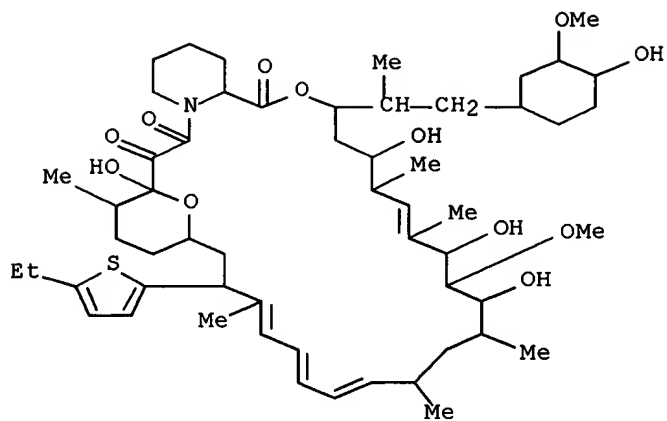
RN 232591-98-9 CAPLUS

CN Rapamycin, 7-demethoxy-27,33-dideoxo-27,33-dihydroxy-7-(5-methyl-2-thienyl)-, (7R,27S,33S)- (9CI) (CA INDEX NAME)

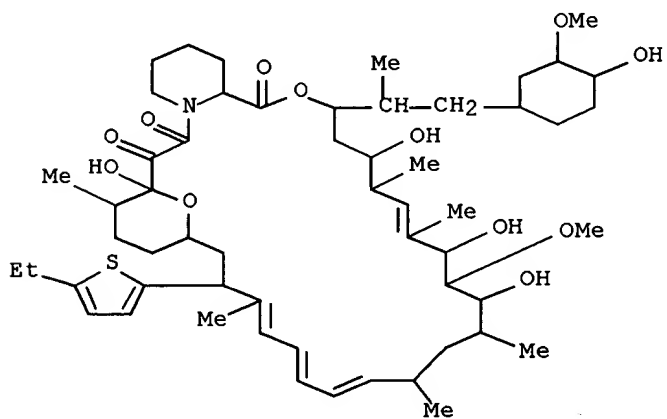


RN 232591-99-0 CAPLUS

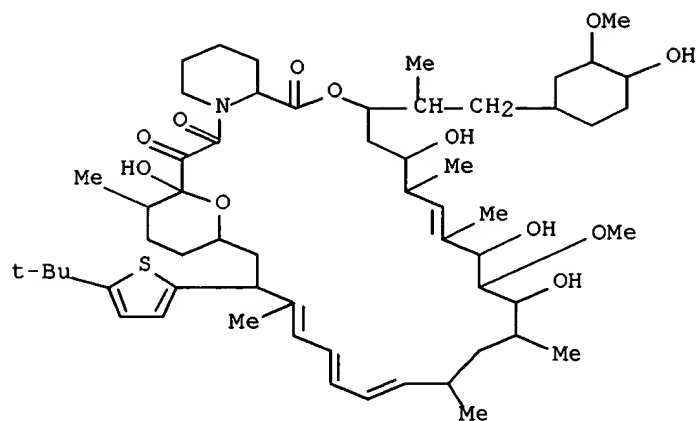
CN Rapamycin, 7-demethoxy-27,33-dideoxo-7-(5-ethyl-2-thienyl)-27,33-dihydroxy-, (27S,33S)- (9CI) (CA INDEX NAME)



RN 232592-00-6 CAPLUS
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 , (7R,27S,33S)- (9CI) (CA INDEX NAME)

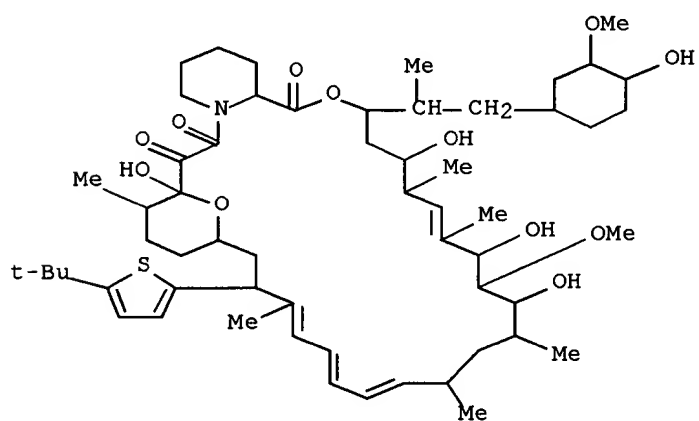


RN 232592-01-7 CAPLUS
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 27,33-dihydroxy-, (27S,33S)- (9CI) (CA INDEX NAME)



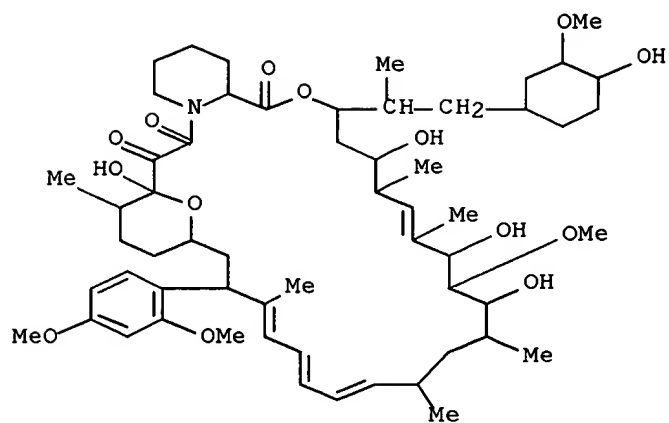
RN 232592-02-8 CAPLUS

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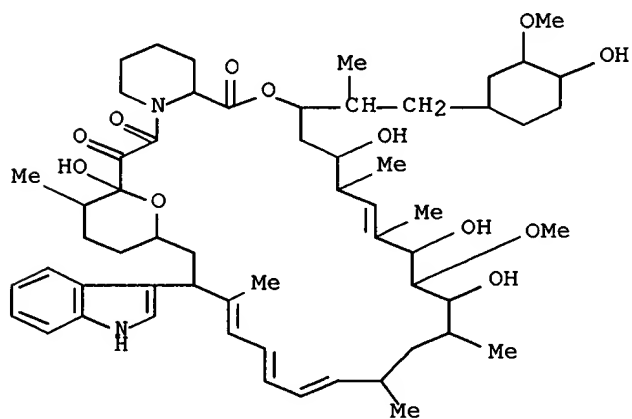
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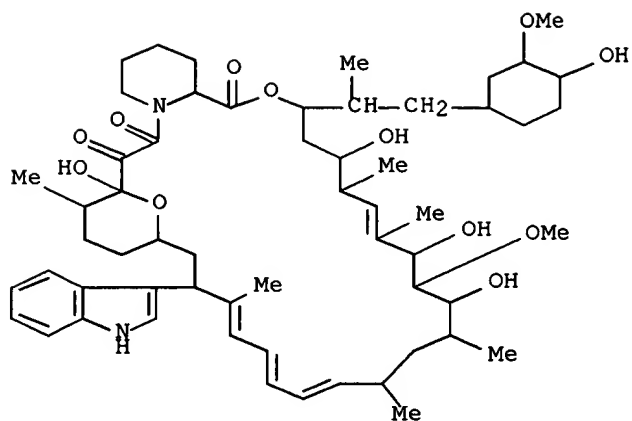
RN 232592-05-1 CAPLUS

CN Rapamycin, 7-demethoxy-27,33-dideoxo-27,33-dihydroxy-7-(1H-indol-3-yl)-, (27S,33S)- (9CI) (CA INDEX NAME)



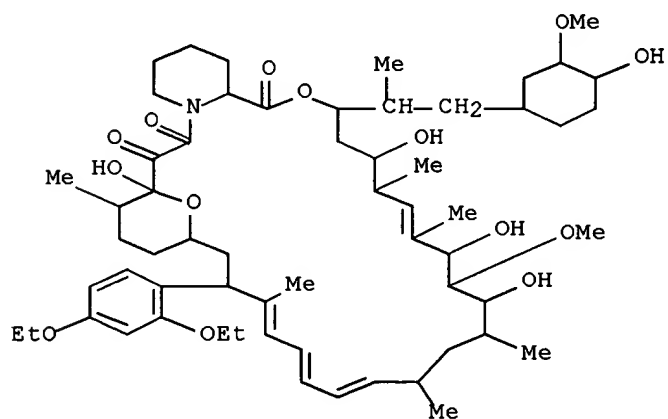
RN 232592-06-2 CAPLUS

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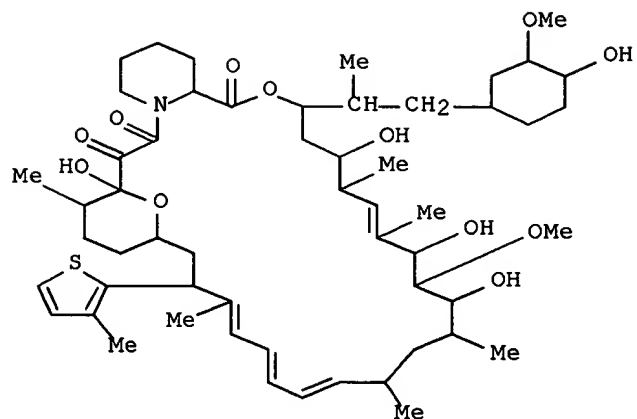
RN 232592-07-3 CAPLUS

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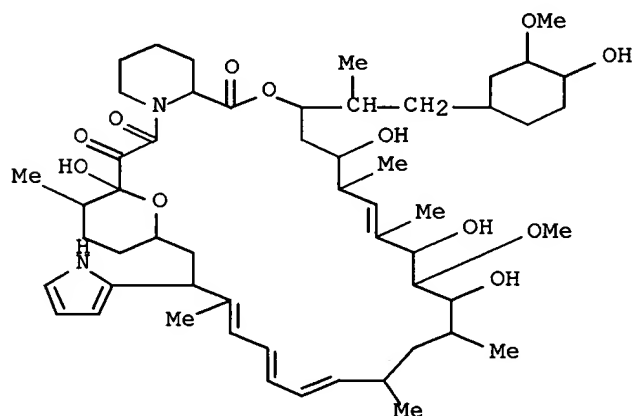
RN 232592-08-4 CAPLUS

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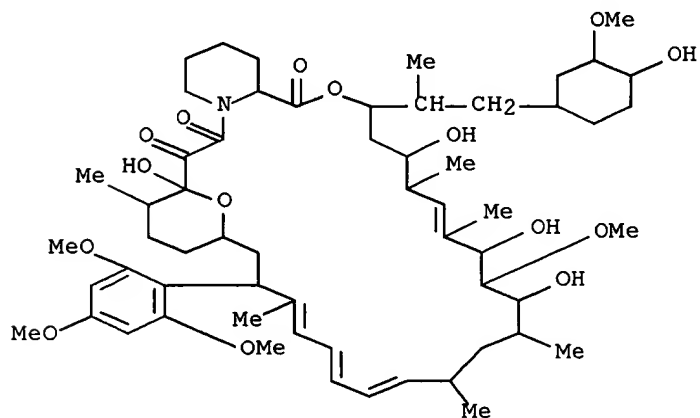
RN 232592-09-5 CAPLUS

CN Rapamycin, 7-demethoxy-27,33-dideoxo-27,33-dihydroxy-7-(1H-pyrrol-2-yl)-, (27S,33S)- (9CI) (CA INDEX NAME)



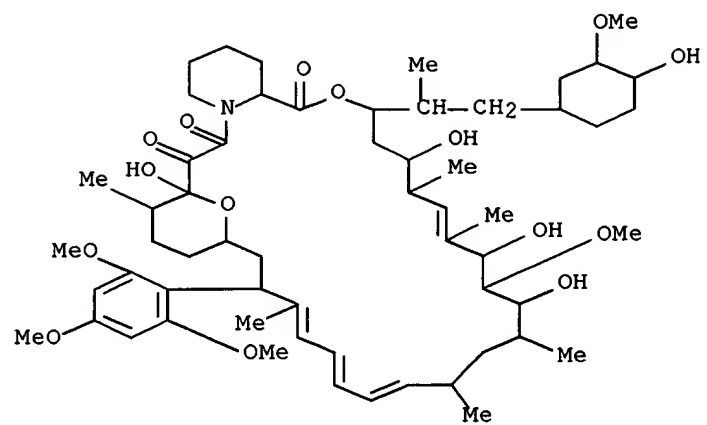
RN 232592-10-8 CAPLUS

CN Rapamycin, 7-demethoxy-27,33-dideoxo-27,33-dihydroxy-7-(2,4,6-trimethoxyphenyl)-, (27S,33S)- (9CI) (CA INDEX NAME)



RN 232592-11-9 CAPLUS

CN Rapamycin, 7-demethoxy-27,33-dideoxo-27,33-dihydroxy-7-(2,4,6-trimethoxyphenyl)-, (7R,27S,33S)- (9CI) (CA INDEX NAME)



L29 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2001 ACS

AN 1998:71140 CAPLUS

DN 128:153966

TI Materials and method for treating or preventing pathogenic fungal infection

IN Holt, Dennis A.; Keenan, Terence P.; Clackson, Timothy P.; Rozamus, Leonard; Yang, Wu; Gilman, Michael Z.

PA Ariad Pharmaceuticals, Inc., USA; Holt, Dennis A.; Keenan, Terence P.; Clackson, Timothy P.; Rozamus, Leonard; Yang, Wu; Gilman, Michael Z.

SO PCT Int. Appl., 76 pp.

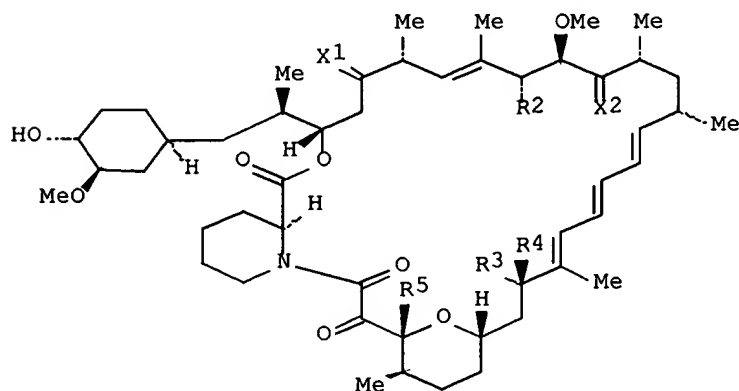
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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	WO 9802441	A3	19980305		
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	RW:	GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			
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	AU 9738858	A1	19980209	AU 1997-38858	19970714
	EP 937082	A2	19990825	EP 1997-936105	19970714
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			
PRAI	US 1996-21624		19960712		
	US 1997-48307		19970530		
	US 1997-50353		19970620		
	WO 1997-US12584		19970714		
OS	MARPAT 128:153966				
GI					



AB Synthesis of rapamycin derivs. (I) [X1 = O, NOR1, .alpha.OH; R1 = H,

alkyl, CH₂CO₂H, CH₂CONH₂; R₂ = OH, F; X₂ = O, .alpha.OH; R₃ or R₄ when the other is H = O-alkyl, OCH₂Ph, NHCO₂Me, NHSO₂Me, (un)substituted aryl, (un)substituted heteroaryl; R₅ = OH, F] for antifungal uses are disclosed.

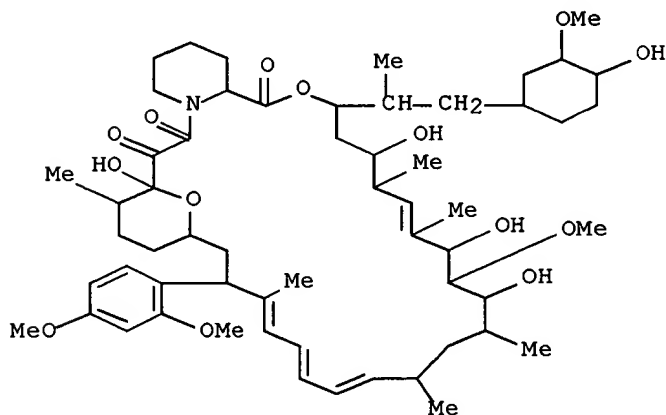
Also disclosed are materials and methods relevant to the identification of non-immunosuppressive antifungal rapamycin derivs. and formulations for drug delivery. Thus, rapamycin 24-(E)-O-methyloxime (II) is prepd. by reacting rapamycin with methoxylamine hydrochloride. II showed an IC₅₀ of 438 nM in FKBPwt FP binding assay and a fold loss in affinity of 190 (vs rapamycin).

IT **202522-60-9P**

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of)

RN 202522-60-9 CAPLUS

CN Rapamycin, 7-demethoxy-27,33-dideoxo-7-(2,4-dimethoxyphenyl)-27,33-dihydroxy-, (27S,33S)- (9CI) (CA INDEX NAME)



IT **158472-50-5P**

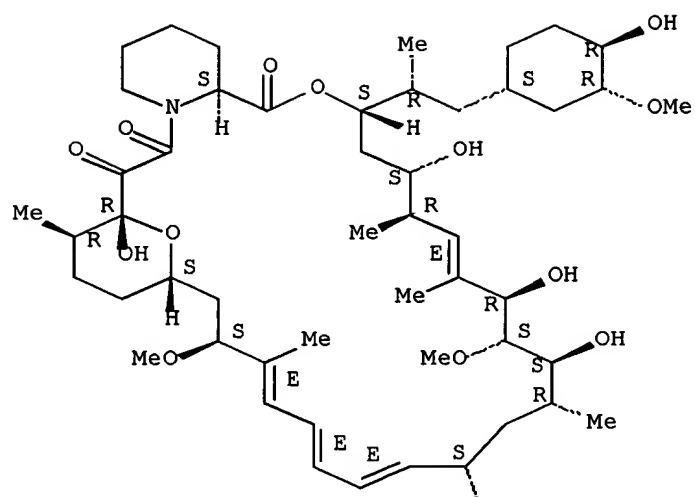
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(synthesis and identification of antifungal rapamycin derivs.)

RN 158472-50-5 CAPLUS

CN Rapamycin, 27,33-dideoxo-27,33-dihydroxy-, (27S,33S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 2-A

Me

L29 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2001 ACS

AN 1994:655471 CAPLUS

DN 121:255471

TI Studies on selective reductions of rapamycin

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SO Tetrahedron Lett. (1994), 35(35), 6469-72

CODEN: TELEAY; ISSN: 0040-4039

DT Journal

LA English

AB The reaction of rapamycin with different reductive agents has been
studied. As expected, the C-14 ketone of the tricarbonyl unit is the

most

electrophilic center in the mol. and could be selectively converted to
either the alc. (Zn/AcOH or DIBAL) or to the C-14 methylene (H₂S,
pyridine/MeOH). Under Luche's conditions the C-14 carbonyl was protected
and redn. took place stereoselectively at both C-24 and C-30

(NaBH₄/CeCl₃)

or exclusively at C-30 (NaBH₃CN/CeCl₃). Selective reaction at C-30 also
took place under Evans conditions with NaBH(OAc)₃. These reactions allow
the selective manipulation of the rapamycin effector domain.

IT 158472-50-5P

RL: SPN (Synthetic preparation); PREP (Preparation)
(regioselective redn. of rapamycin)

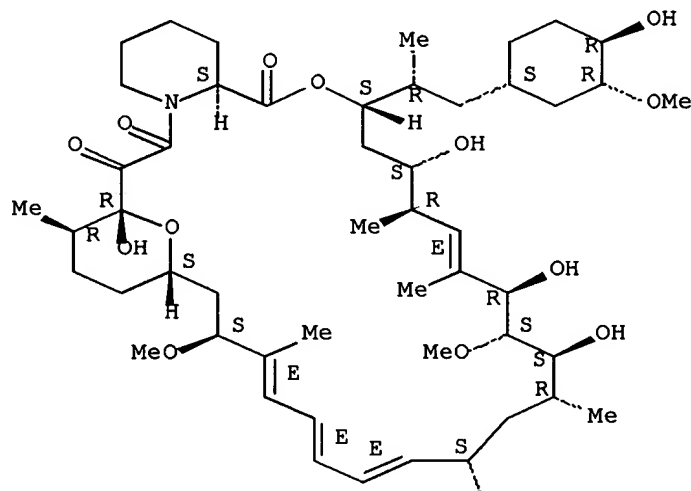
RN 158472-50-5 CAPLUS

CN Rapamycin, 27,33-dideoxo-27,33-dihydroxy-, (27S,33S)- (9CI) (CA INDEX
NAME)

Absolute stereochemistry.

Double bond geometry as shown.

PAGE 1-A



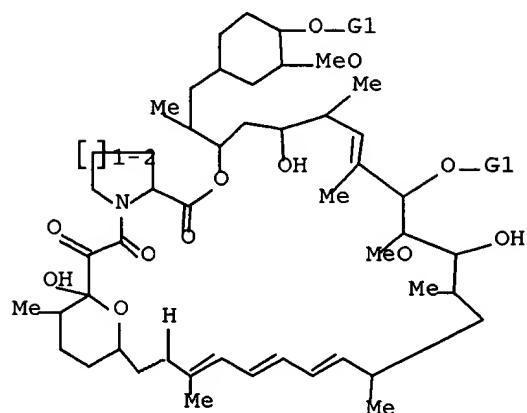
PAGE 2-A

Me

=> d 125; d 12; d his

L25 HAS NO ANSWERS

L25 STR

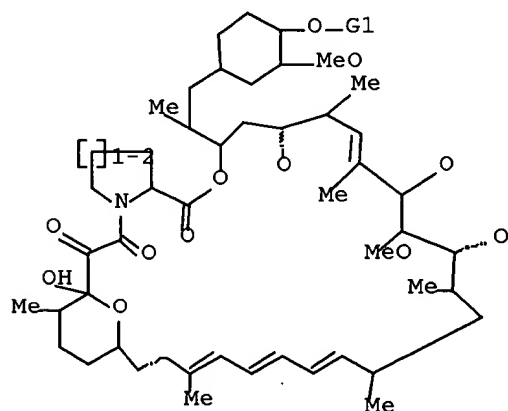


G1 H, Ak

Structure attributes must be viewed using STN Express query preparation.

L2 HAS NO ANSWERS

L2 STR



G1 H, Ak

Structure attributes must be viewed using STN Express query preparation.

(FILE 'HOME' ENTERED AT 18:15:15 ON 12 APR 2001)

FILE 'REGISTRY' ENTERED AT 18:15:48 ON 12 APR 2001

L1 SCREEN 1821 OR 1822 OR 1823 OR 1824

L2 STRUCTURE UPLOADED

L3 QUE L2 AND L1 AND L1

L4 34 S L3

L5 695 S L3 FUL

FILE 'STNGUIDE' ENTERED AT 18:16:57 ON 12 APR 2001

FILE 'REGISTRY' ENTERED AT 18:18:32 ON 12 APR 2001

L6 SCREEN 1821 OR 1822 OR 1823 OR 1824

L7 STRUCTURE UPLOADED
L8 QUE L7 AND L6 AND L6
L9 32 S L8 SAM SUB=L5
L10 624 S L8 FUL SUB=L5
L11 SCREEN 1821 OR 1822 OR 1823 OR 1824
L12 STRUCTURE UPLOADED
L13 QUE L12 AND L11 AND L11
L14 0 S L13 SAM SUB=L5
L15 2 S L13 FUL SUB=L5

FILE 'CAPLUS' ENTERED AT 18:21:17 ON 12 APR 2001
L16 4 S L15

FILE 'STNGUIDE' ENTERED AT 18:22:25 ON 12 APR 2001

FILE 'REGISTRY' ENTERED AT 18:30:31 ON 12 APR 2001
L17 SCREEN 1821 OR 1822 OR 1823 OR 1824
L18 STRUCTURE UPLOADED
L19 QUE L18 AND L17 AND L17
L20 32 S L19 SAM SUB=L5
L21 624 S L19 FUL SUB=L5

FILE 'CAPLUS' ENTERED AT 18:32:38 ON 12 APR 2001
L22 1388 S L21
L23 1388 S L5

FILE 'STNGUIDE' ENTERED AT 18:33:43 ON 12 APR 2001

FILE 'REGISTRY' ENTERED AT 18:37:26 ON 12 APR 2001
L24 SCREEN 1821 OR 1822 OR 1823 OR 1824
L25 STRUCTURE UPLOADED
L26 QUE L25 AND L24 AND L24
L27 1 S L26 SAM SUB=L5
L28 25 S L26 FUL SUB=L5

FILE 'CAPLUS' ENTERED AT 18:38:23 ON 12 APR 2001
L29 4 S L28

FILE 'STNGUIDE' ENTERED AT 18:40:28 ON 12 APR 2001